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HERCULES

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September 25, 1997

VIA OVERNIGHT MAIL

Mr. Leo F. Francendese
On - Scene Coordinator
U.S. EPA Region IV
Atlanta Federal Center
100 Alabama Street
Atlanta, Georgia 30303

RE: **Terry Creek Dredge Spoil Site - Brunswick, GA**
New Information on Toxaphene Toxicity Potential

Dear Leo:

Hercules has been developing data to support a reassessment of the carcinogenic potential of toxaphene. Enclosed for your information is a copy of "TOXAPHENE. BASIS FOR A CHANGE IN THE CANCER CLASSIFICATION AND FOR A CHANGE IN AND RECALCULATION OF THE CANCER POTENCY FACTOR", Volumes I and II, Judith W. Hauswirth, Ph.D. Jellinek Schwartz & Connolly, September 17, 1997. Based on an evaluation of the new data using current scientific standards, this document proposes that the Cancer Slope Factor (CSF) be changed from 1.1 to 0.16 $(mg/kg/day)^{-1}$. A copy has been sent to the Superfund Docket for the Terry Creek Dredge Spoil Areas/Hercules Outfall, Brunswick, Ga. Also for your information, Hercules is currently in discussions with the appropriate EPA Headquarters personnel regarding the reassessment and expects to meet with them in the third quarter of this year.

Please contact me if you have any questions regarding these documents. Hercules has discussed these documents with appropriate GaEPD personnel an meeting with them and EPA regional scientists to discuss toxaphene toxicity .

Sincerely,

Timothy D. Hassett
Staff Environmental Engineer
Safety, Health, and Environment Department

TDH/
terkdoc.003

w/enclosures

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TOXAPHENE:

BASIS FOR A CHANGE IN AND RECALCULATION OF THE CANCER POTENCY FACTOR

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VOLUME I OF II

TOXAPHENE: BASIS FOR A CHANGE IN AND RECALCULATION OF THE CANCER POTENCY FACTOR

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TOXAPHENE:
BASIS FOR A CHANGE IN AND RECALCULATION OF THE CANCER POTENCY FACTOR

EXECUTIVE SUMMARY

This document presents Hercules Incorporated's (Hercules) rationale and justification for concluding that the cancer potency factor for toxaphene should be changed. The Agency's current approach uses liver tumor data from a study conducted by Litton Bionetics (1978) for Hercules. Alternatively, Hercules proposes that a mouse oncogenicity study conducted by the National Cancer Institute (NCI, 1979) on toxaphene is more appropriate for estimating a cancer potency factor. This conclusion is based on two factors. First, Hercules believes that the Litton study is unsuitable for risk assessment purposes because the diagnostic criteria used for liver tumors at the time the study was conducted have changed and because, based on historical control data, the observed liver tumor response is not biologically relevant. Second, Hercules, through an independent contractor, convened an independent pathology working group (PWG) to review the liver slides from the NCI mouse oncogenicity study according to current diagnostic criteria that resulted in a dramatic change in the incidence data, particularly in the ratio of benign to malignant liver tumors.

The proposed potency factor derived from the most sensitive response in the animal bioassays—namely, liver adenoma/carcinoma mouse tumor data from the NCI study as reevaluated by the PWG—is calculated to be 0.16 $(\text{mg/kg/day})^{-1}$ (geometric mean of potency factors derived from the male and female liver tumor data). The calculation of this upper bound on the cancer potency for toxaphene includes the data on the time of the observation of each mouse, the conservative low-dose linear extrapolation below the benchmark dose (the LED_{10}), and the current default procedures for interspecies extrapolation between mice and humans.

Hercules proposes that a potency factor of 0.16 $(\text{mg/kg/day})^{-1}$ be used in toxaphene risk assessments if EPA continues using a linear approach.

TOXAPHENE:
BASIS FOR A CHANGE IN AND RECALCULATION OF THE CANCER POTENCY FACTOR

I. INTRODUCTION

Toxaphene is an organochlorine pesticide belonging to a class of compounds known as polychlorinated bicyclic terpenes. Toxaphene was used as an insecticide on many types of fruit, vegetable, and field crops in the United States before 1982. Its major registrations with the U.S. Environmental Protection Agency (EPA or the Agency) were canceled in 1982 because of EPA's concerns about human and environmental safety; final cancellations occurred in 1990. Because toxaphene is persistent, potential soil and water contamination by the compound continue to be the subject of regulatory and judicial attention at many sites around the country.

Toxaphene is presently considered a category B_2 oncogen (probable human carcinogen) by EPA. For its classification, EPA relied on the results of three lifetime feeding studies—two in mice and one in rats. EPA found the administration of toxaphene to be associated with an increased incidence of liver tumors (adenomas or neoplastic nodules and carcinomas) in male and female mice, and also with an increased incidence of thyroid tumors (primarily adenomas) in male and female rats. The category B_2 classification was based on criteria outlined in EPA's Carcinogen Risk Assessment Guidelines (EPA, 1986). The toxaphene tumor data met criteria in (a) multiple species and (b) multiple experiments for sufficient evidence of animal carcinogenicity required for a B_2 classification. EPA calculated a potency factor of 1.1 $(mg/kg/day)^{-1}$ based on the mouse liver tumor data.

The purpose of this document is to provide EPA with a scientifically based rationale for changing the cancer potency factor for toxaphene. Hercules strongly believes that toxaphene should be regulated by a Margin of Exposure (MOE) approach; however, if the Agency continues to believe that toxaphene is a non-threshold oncogen, Hercules proposes, based on the information in this paper, that the Agency regulate toxaphene using a cancer potency factor of 0.16 $(mg/kg/day)^{-1}$ instead of the factor [1.1 $(mg/kg/day)^{-1}$] presently found in IRIS.

II. BASIS FOR A CHANGE IN AND THE CANCER POTENCY FACTOR

Although Hercules believes a nonlinear threshold model is more appropriate for estimating cancer risk, Hercules also notes that the current linear (potency factor) approach used by EPA is overly conservative. Hercules believes that this aspect must be addressed if EPA's use of the linear approach persists.

The purpose of this part of the document is to provide the Agency with a scientifically sound basis for changing the cancer potency factor for toxaphene. Hercules believes that such a change is justified based primarily on the unsuitability of the study by Litton (1978) currently used by the Agency (as found in IRIS) for calculating the cancer potency factor. Hercules strongly believes that the NCI bioassay (1979) is the appropriate study to use for this calculation and, consequently, has recalculated the potency factor using the reevaluated tumor incidence data from this study. The rationale for Hercules' conclusions is discussed in detail in the following sections.

A. Background Information

1. Toxaphene Oncogenicity Studies

Four separate oncogenicity studies have been conducted on toxaphene: two in mice, one conducted by Litton Bionetics (Litton, 1978) for Hercules and the other by Gulf South Research Institute (Gulf South) for NCI (NCI, 1979); one in rats conducted by Gulf South for NCI (1979); and one in hamsters conducted by Litton (1979) for Hercules. In the Litton mouse study (1978), $B6C3F_1$ mice (55/sex/group) were fed diets containing toxaphene for a period of 18 months, and then placed on untreated diets for 6 additional months. Dosage levels were 0, 7, 20, and 50 ppm. No treatment-related effects were seen on survival or clinical signs. Body weights and food consumption were not monitored in this study.

The two mouse studies were conducted with the same batch of toxaphene (Lot No. X-16189-49) and according to similar protocols with respect to the dosing regimen. The animals used in these studies were obtained either from Charles River Laboratories (NCI study) or the Frederick Cancer Research Institute (Litton study) and were bred from the same original parental generations obtained from the National Institutes of Health.

It is worthwhile to note that during this time period, Litton was also used by NCI as a contract laboratory for conducting oncogenicity studies. This is an important factor when considering the appropriate use of historical control data (see section II.B.2 below on historical control data).

In the NCI mouse study (1979), $B6C3F_1$ mice (50/sex/group, except the matched control of 10/sex/group) were fed toxaphene for a period of 80 weeks, and then placed on untreated diet for 10-11 weeks. The initial doses were 160 and 320 ppm; because of several deaths, they were lowered at 19 weeks to 80 and 160 ppm, respectively. Based on time-weighted averages, the dosage levels were 0, 99, and 198 ppm.

In the NCI rat study (1979), Osborne-Mendel rats (50/sex/group) were fed diets containing toxaphene for a period 80 weeks, and then placed on untreated diets for an additional 28 or 30 weeks. The time-weighted average dosage levels tested were 0, 556, and 1112 ppm for males, and 0, 540, and

1080 ppm for females. Because of clinical signs of toxicity (hyperactivity) in high-dose males at week 2, both dosage levels were dropped by half. At 52 weeks, both high-dose males and high-dose females developed generalized body tremors and doses were again halved. The dosage levels by study week for males and females are summarized in Table 1.

Table 1. Dosing Regimen in the NCI Rat Oncogenicity Study

Sex and Test Group	Toxaphene in the Diet (ppm)	Week of Study	Time-Weighted Average Dose (ppm)
Males			
Low Dose	1,280	0-2	556
	640	2-52	
	320	52-80	
	0	80-termination	
High Dose	2,560	0-2	1112
	1,280	2-52	
	640	52-80	
	0	80-termination	
Females			
Low Dose	640	0-52	540
	320	52-80	
	0	80-termination	
High Dose	1,280	0-52	1,080
	640	52-80	
	0	80-termination	

In the hamster study (Litton, 1979), ARS Golden Syrian hamsters (51/sex/group) were placed on diets containing 0, 100, 300, or 1000 ppm toxaphene. Males were maintained on treated diet for 21.5 months and females for 18 months. Treatment-related effects seen in this study consisted of decreased body weights in males at both treatment levels, and "megahepatocytes" upon histologic examination of the liver at the high-dose level in males. The administration of toxaphene was not associated with an increase in any tumor type in hamsters; therefore, it can be concluded that toxaphene is not oncogenic to hamsters.

The incidence of relevant tumors seen in each of these studies is summarized in Table 2.

The tumors that were statistically increased include mouse liver tumors in 50-ppm dosed males (Litton, 1978) and in males and females dosed at 99 and 198 ppm (NCI, 1979), and thyroid tumors in male and female rats at 1112 ppm (NCI, 1979). Kidney tumors were also slightly increased in the NCI rat study (1979) in males, but the increase was neither statistically significant nor dose-related.

Table 2. Incidence of Relevant Tumors Seen in Mice and Rat Toxaphene Studies

Tumor Type	Dosage Level (ppm)			
Mice		**Males—Litton**		
Liver				
	0	**7**	**20**	**50**
Adenoma	3/53	0/54	2/53	11/51
Carcinoma	7/53	11/54	12/53	12/51
Total[a]	10/53	10/54	12/53	18/51*
		Females—Litton		
Adenoma	1/53	1/53	1/52	3/52
Carcinoma	1/53	1/53	3/52	3/52
Total	2/53	2/53	4/52	6/52
		Males—NCI		
	0[b]	**0[c]**	**99**	**198**
Neoplastic Nodule	2/10	3/48	6/49	0/46
Carcinoma	0/10	4/48	34/49**	45/46**
Total	2/10	7/48	40/49**	45/46**
		Females—NCI		
Neoplastic Nodule	0/9	0/48	13/49	6/49
Carcinoma	0/9	0/48	5/49*	34/49**
Total	0/9	0/48	18/49*	40/49**
		Males—NCI		
Rats				
Thyroid				
	0[b]	**0[d]**	**556**	**1112**
Follicular cell				
adenoma	1/7	—	7/41	7/35
carcinoma	0/7	—	0/41	2/35
combined	1/7	2/44	7/41	9/35**
Kidney				
Tubular cell adenoma	0/9	—	2/45	1/45
Mixed cell malignant	0/9	—	1/45	1/45
Hematoma	0/9	—	0/45	1/45
		Females—NCI		
Thyroid				
	0[b]	**0[d]**	**540**	**1080**
Follicular cell adenoma	0/6	1/46	1/49	7/42*

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[a] In determining total tumors no animal was counted twice, (e.g., if an animal had both an adenoma and a carcinoma, only the carcinoma was counted.)

[b] Concurrent control.

[c] Pooled controls from five studies (toxaphene, gardona, malathion, lindane, and phosphamidon) conducted at Gulf South Research Institute by NCI. The gardona, malathion, lindane and phosphamidon studies were conducted at approximately the same time as the toxaphene study.

[d] Pooled controls from six studies (toxaphene, captan, chloramben, lindane, malathion, and picloram) conducted by NCI.

* $P<0.05$; **$p<0.01$. Not all tumor types were statistically analyzed by NCI or Litton. Where significance was determined, it is noted in the table.

2. Additional Information on Toxaphene Toxicity and Mechanism for Tumor Induction

a. Tumor Mechanistic Data

Mouse Liver Tumors: Two hypotheses were investigated by Hercules to determine a possible mechanism by which toxaphene induces liver tumors in mice. The first hypothesis examined was whether toxaphene was inducing these tumors through liver peroxisome proliferation. Because induction of hepatic cytochrome P450 41A (41A) has been found to be associated with peroxisome proliferators, the effect of treating mice with toxaphene on this isozyme of cytochrome P450 was determined. [Toxaphene is known to induce cytochrome P450s in a pattern similar to phenobarbital (PB) (Hodgson et al., 1980).] In this same study, livers from toxaphene-treated mice were frozen and DNA was extracted from them at a later date to determine whether toxaphene induced DNA adduct formation (second hypothesis). The method used to measure DNA adducts was the method of Reddy and Randerath (1986) using nuclease P1-enhanced DNA^{32}P postlabeling. Three to four male mice per group were treated with either 0, 10, 50, or 100 mg/kg/day toxaphene by corn oil gavage for seven consecutive days. Clofibrate, a known peroxisome proliferator, served as the positive control for peroxisome proliferation. These investigations were carried out at Rutgers University by Drs. C. C. Hedli and Robert Snyder, and a summary of their findings can be found in Appendix 1.

Clofibrate caused a significant induction in the amount of hepatic 41A; however, toxaphene had no effect on the hepatic levels of this cytochrome P450 isozyme. Toxaphene did induce cytochrome P450 2B, which is typical of the PB-like family of P450 inducers. In addition, no evidence for DNA adduct formation was found in the liver of toxaphene-treated mice.

Although the information derived from the above studies is not conclusive, it does give some indication of what is not the mechanism of mouse liver tumor induction by toxaphene. Toxaphene does not appear to be a peroxisome proliferator, nor does it appear to interact directly with hepatic DNA.

It is relevant to the toxaphene-induced liver tumors to note that Butler (1996) has recently proposed that hepatocellular adenomas associated with microsomal enzyme inducers should not be considered a carcinogenic response to the chemical. According to Butler, these tumors have a different histologic appearance than spontaneously occurring mouse liver tumors with increased eosinophilic cytoplasm (not basophilic) and pleomorphic (not uniform) nuclei. Butler further states that liver tumors (adenomas and carcinomas) induced by genotoxic carcinogens and peroxisome proliferators are histologically similar to spontaneously occurring tumors. Owen (1996), when reviewing Butler's hypothesis and other possible mechanisms of liver tumor formation resulting from administration of PB and other microsomal enzyme inducers, concluded that "dose-related epigenetic mechanisms of tumor induction involved in the carcinogenesis of MFO (mixed-function oxidizers or microsomal enzyme inducers) in mice have thresholds below which tumors will not occur [nonlinear threshold]." Ward (1996) expresses hope that Butler's proposal will stimulate further research in this area.

Another factor that has been found to be important in liver tumor induction in mice is calorie restriction (Blackwell, et al. 1995; Muskhelishvili, et al. 1995). Fu et al. (1994) has shown that calorie restriction in B6C3F$_1$ neonatal mice drastically reduces the number of 6-nitrochrysene-induced liver tumors. In the toxaphene studies, toxaphene was added to the diet in corn oil (250 mL/kg) which added to the caloric burden of the diet and could have contributed to the susceptibility of these mice to both spontaneous and chemically induced liver tumors.

Both caloric restriction and Butler's proposal concerning the histologic properties of liver tumors induced by microsomal enzyme inducers raise significant questions about the relevance to man of the induction by toxaphene of benign liver tumors in mice.

Thyroid Tumors: As discussed above, toxaphene is known to be hepatic microsomal enzyme inducer similar to PB. PB also induces the incidence of thyroid follicular cell tumors in rats (McClain et al. 1988). It does this through a mechanism mediated through the hypothalamic-pituitary-thyroid (HPT) axis. Because of the similarity of responses, Hercules decided to conduct a study to determine whether toxaphene caused a perturbation in the HPT axis, thereby leading to the formation of thyroid follicular cell tumors in rats. Such a mechanism for the induction of thyroid tumors has recently been proposed by EPA as having a nonlinear threshold (EPA, 1996b). EPA does not reject this rat model for human thyroid carcinogenesis but allows that it appears "that quantitatively humans are less sensitive than rodents" to thyroid-pituitary disruption. Certain thyroid carcinogens, meeting the criteria set forth by EPA, are regulated using an MOE, rather than linear extrapolation (EPA, 1996b). EPA's proposed thyroid tumor policy was recently endorsed by an outside Science Advisory Board convened by the Agency (report sent to EPA Administrator Carol Browner on December 24, 1996; EPA-SAB-EHC-LTR-97-002).

The 28-day mechanistic study was conducted in Crl:Cd BR (Sprague-Dawley) rats (Waritz, et al. 1996). A group of 40 male rats was administered toxaphene by gavage at a dosage level of 100 mg/kg/day. Because of two deaths within the first four days of treatment, the dosage level was dropped to 75 mg/kg/day. A group of 40 male rats served as controls and were dosed by gavage with vehicle (corn oil). Groups of 10 animals were bled on days 1, 8, 15, and 29 for determination of thyroid stimulating hormone (TSH), triidothyronine (T_3), thyroxine (T_4), and reverse T_3, then necropsied; thereafter, the thyroid/parathyroid and pituitaries were examined grossly and histologically. Brain, thyroid/parathyroid, and pituitary were weighed.

Both absolute and relative thyroid/parathyroid weights were increased in the toxaphene-treated rats compared to the controls after 7, 14, and 28 days of treatment. TSH levels were increased at these same time periods in the treated rats. Levels of T_3 and T_4 were slightly decreased or similar to the control values. Possibly treatment-related effects on T_3 were seen at day 15. Histologically, in the control animals neither follicular cell hypertrophy or hyperplasia was seen. At day 8, 7/10 and 1/10 of the toxaphene-treated rats had follicular cell hypertrophy and hyperplasia, respectively. By day 15, the incidence of each of these findings was 7/10 and 9/10, respectively, and by day 29, the incidence was 8/8 for both findings.

The results of this study support the hypothesis that toxaphene induces thyroid tumors through a perturbation of the HPT axis, resulting in increased circulating TSH levels and excessive stimulation of the thyroid gland. This mechanism has been shown to have a nonlinear threshold.

Kidney Tumors: Although the increase in kidney tumors was not statistically increased in male rats in the NCI study, Hercules felt compelled to determine the mechanism, if any, by which toxaphene induced these tumors. As a result Hercules contracted Hazleton Washington to conduct the in-life portion of a 28-day study in which male and female Sprague-Dawley rats were fed 825 and 550 ppm toxaphene in the diet, respectively. Experimental Pathology Laboratories, Inc. (Busey, 1994) conducted the histopathology examination of the kidney and Dr. James Swenberg subsequently evaluated the kidney slides from this study immunohistochemically for alpha-2u-globulin. Dr. Swenberg's report of his evaluation of the kidneys can be found in Appendix 2. (The positive control used for comparison was d-limonine.) Dr. Swenberg found that the kidneys of 7/10 male rats from the toxaphene study had prominent numbers of large hyaline droplets in the proximate convoluted tubules that stained positively for alpha-2u-globulin. Four of the toxaphene-treated male rats also had casts at the junction of the inner and outer strip of the medulla that stained positively for alpha-2u-globulin. Dr. Swenberg concluded that these results demonstrated very strong evidence that toxaphene induces alpha-2u-globulin nephropathy.

These results provide convincing support that the mechanism by which kidney tumors were induced in a few male rats in the NCI study were the result of alpha-2u-globulin nephropathy and not a direct action of toxaphene on the kidney. EPA (1991) has determined that alpha-2u-nephropathy should not be used for the purposes of human risk assessments.

b. Other Toxicity Associated with Toxaphene

This section contains a general summary of toxicity, other than carcinogencity, associated with toxaphene exposure in experimental animals. A more detailed description of toxaphene-related toxicity can be found in the recently published ATSDR document on toxaphene (Appendix 3).

Toxaphene-induced toxicity results from a combination of factors, but the effect leading to its efficacy as an insecticide is its toxic effects on the nervous system of target pests. The central nervous system (CNS) in mammalian species is also a target for toxaphene, but the mammalian system is less sensitive. In experimental animals toxaphene administration results in a stimulation of the CNS. This stimulation is proposed to be the result of the noncompetitive inhibition of a gamma-aminobutyric acid (GABA)-dependent chloride ion channel. GABA is believed to be an inhibitory neurotransmitter. Thus, blocking its action leads to over-activity of those neurons whose activity is modulated by GABA.

Toxaphene exhibits moderate acute oral, dermal, and inhalation toxicity in rodents. It is a dermal irritant and mildly irritating to the eye. Subchronic toxicity studies have been conducted with toxaphene in rats, dogs, and mice. Hepatic, thyroid, and renal toxicity are the principal findings associated with subchronic exposure in rats, hepatic and renal findings in dogs, and hepatic toxicity in mice.

Chronic toxicity studies on toxaphene have been conducted in mice, rats, dogs, and hamsters. As already discussed, toxaphene is oncogenic in mice (liver) and rats (thyroid), but not in hamsters. In addition to oncogenicity, toxaphene causes hepatic hypertrophy accompanied by increased microsomal enzyme activity and other histological changes in liver cells. The thyroid, kidneys, spleen, and adrenal gland have also been identified as target organs of toxaphene-induced toxicity.

Toxaphene showed no evidence of teratogenicity based on developmental toxicity studies in rats and mice. Developmental toxicity (decreased fetal weights, delayed ossification) was seen only at maternally toxic dose levels. Equivocal evidence of reversible behavioral deficits was seen following perinatal exposures to toxaphene.

Multigeneration reproduction studies have been conducted on toxaphene in both rats and mice. The results of these studies indicate that orally administered toxaphene does not adversely affect male or female reproductive processes.

The complexity of toxaphene makes it difficult to understand its metabolism fully. It appears that all of its components undergo rapid metabolism, yet each component has its own rate of biotransformation. Toxaphene is rapidly and extensively degraded in mammals following oral administration. Results of *in vivo* and *in vitro* studies indicate that the principal metabolic pathways involve dechlorination, dehydrodechlorination, and oxidation. Conjugation is also likely, but is not a major route of metabolism.

c. Genotoxicity

The genotoxicity of toxaphene has been studied in a wide variety of test systems. The results of these studies are summarized in Table 3.

Table 3. The Results of Genotoxicity Testing of Toxaphene

Study Type	Results	Reference
Ames Salmonella Assay		
Strains TA 1535, 1537, 1538	Negative	Brusick, 1977
		Hooper et al., 1979
		Mortelmans et al., 1986
Strain TA 98	Negative	Brusick, 1977
	Positive	Brusick, 1977
		Mortelmans et al., 1986
	Pos., Neg	Hooper et al., 1986
Strain TA 100	Negative	Brusick, 1977
	Positive	Mortelmans et al., 1986
		Hooper et al., 1979
Saccharomyces cerevisiae strain D4	Negative	Brusick, 1977
E. coli strain WP2(s) lambda	Positive	Houk and DeMarini, 1987
Sister chromatid exchange (SCE)		
human lymphoid cells	Positive	Sobti et al., 1983
Dominant lethal in mice	Negative	Epstein et al., 1972
SCE in chinese hamster lung (DON) cells	Positive	Steinel, et. al, 1990
E. coli K-12		
DNA breaks	Negative	Griffin and Hill, 1978
Chromosomal aberrations		
human leukocytes	Negative	EPA, 1978
human lymphocytes	Positive	Samosh, 1974

The mutagenicity test results were mixed. Toxaphene was negative in three strains of Salmonella (TA 1535, TA 1537, and TA 1538), but both positive (albeit weakly) and negative (with and without metabolic activation) in two other strains (TA 98 and TA 100). Several sources of metabolic activation have been used in the Ames assay, including liver preparations from hamster, mouse, rat, and human. The results using the human liver preparation were negative in both TA 98 and TA 100, as were the liver preparations from other sources when corn oil was used as the vehicle in the assay. The results of the various Ames

Salmonella assays conducted on toxaphene (with and without metabolic activation) are summarized in Table 4.

Table 4. Ames Test Results With Toxaphene

	TA-98					TA-100					
SOLVENT	NO S-9[a]	HAL S-9	ML S-9	RL S-9	HUL S-9	NO S-9	HAL S-9	ML S-9	RL S-9	HUL S-9	Reference[b]
DMSO[c]	+	-	NT[c]	+	NT	+	+	NT	+	NT	1
DMSO	-	NT	NT	NT	NT	±	NT	NT	NT	NT	2
CORN OIL	+	-	-	-	-	±	-	-	-	-	2
?[c]	+	NT	+	+	NT	+	NT	+	+	NT	3

[a] S-9 metabolic activation system (post-mitrochondrial liver fraction). NO = None, HAL = Hamster, ML = mouse, RL = rat, HUL = human. Animal S-9 used by Mortelmans et al. (1986) and by Brusick (1977) was obtained from animals induced with Aroclor 1254. Hooper et al. (1979) did not report whether their S-9 was prepared from induced animals.

[b] Ref. 1 is Mortelmans et al. (1986); Ref. 2 is Brusick (1977), and Ref. 3 is Hooper et al., (1979)

[c] DMSO = dimethyl sulfoxide; ? = solvent not given; NT = not tested

The information available for review for two of the three references discussing the Ames assay results on toxaphene is minimal. One paper reports on the results of studies conducted by Hooper, et al. (1979) and contains little actual data for the various toxaphene concentrations tested (some data are graphically presented while other data are presented in References and Notes to the paper and only as ranges). The solvent used in this study is not specified and it is not clear if TA 98 was tested in the presence of metabolic activation. However, the addition of metabolic activation decreased the mutagenic activity (number of revertant colonies per plate) of toxaphene toward TA 100 by 50%.

The other literature reference (Mortelmans et al., 1986) contains the testing results on 270 chemicals and compiles data obtained from several testing laboratories. This study program was supported by the National Toxicology Program. Detailed information is provided in the reference on the methodology used by the various testing laboratories used by NTP. The chemicals were sent to the testing laboratories coded such that the laboratory did not know which chemical it was testing. The code was broken once the results had been sent to NTP. No raw data are available in the publication, only summary data for each Salmonella strain tested with and without metabolic activation (rat and hamster). The solvent used in this study was DMSO. Toxaphene was positive in the presence and absence of metabolic activation in TA 100 and TA 98 (positive in the presence of rat S9 only); however, the presence of S9 reduced the mutagenic activity (number of revertant colonies per plate).

The third reference is to work contracted by Hercules with Litton Bionetics, Inc. (Brusick, 1977) on toxaphene and is an unpublished report. In this study, toxaphene was positive without metabolic activation in strains TA 98 and 100; however, metabolic activation obliterated the positive response entirely.

Taken together the results of Ames Salmonella assays indicate that toxaphene is mutagenic toward Salmonella strains TA 100 and TA 98, but that the presence of metabolic activation in the test system reduces toxaphene's mutagenic activity toward these two Salmonella strains.

Toxaphene was negative for mutation induction in *Saccharomyces cerevisiae* strain D4, dominant lethals in mice, DNA breaks in *E. coli* K-12 DNA, and chromosomal aberrations in human leukocytes (Table 3). Toxaphene was tested for mutagenic potential in *Saccharomyces* in conjunction with the Ames assay by Litton Bionetics (Brusick, 1977). The results with and without activation were clearly negative.

In the mouse dominant lethal study (Epstein, et al., 1972), toxaphene was one of 174 test agents. The purpose of the study was to develop standard criteria for the evaluation of the mouse dominant lethal assay. Toxaphene was tested by two routes of exposure, intraperitoneal and orally, at dose levels of 36 and 180 mg/kg (single), and 40 and 80 mg/kg/day (5 daily doses), respectively. Deaths were seen at all dose levels, except 36 mg/kg, indicating that the dose levels tested were adequate for detecting dominant lethals. Toxaphene was clearly negative by the most stringent criteria.

In the *E. coli* K-12 DNA assay (Griffin and Hill, 1978), a purified and radiolabeled circular plasmid is incubated with the test material for up to 28 days and then breaks in the DNA are determined using density gradient separation of fragments. Three known alkylating agents and mutagens were used to validate the method. These included MMS, EMS, and MNNG and each produced a positive, dose-related response in this assay. The results using toxaphene (1 mg/ml) were negative.

The third negative study was sponsored by EPA (1978) and involved monitoring workers that applied toxaphene to cotton (Texas), cattle (Colorado), and onions (Colorado) for chromosomal aberrations in blood (leukocytes). Blood was drawn immediately after exposure from workers and from appropriate unexposed individuals. The analyses for chromosomal aberrations were performed blind. The results indicate no increase in the incidence of aberrations in the blood of toxaphene exposed individuals.

The four remaining studies listed in Table 3 were positive. These included assays for sister chromatid exchange (SCE) in human lymphoid cells, for SCE in Chinese hamster lung cells (DON), induction of prophage lambda, and for chromosomal aberrations in human lymphocyte cultures. In the human lymphoid cell study (Sobti, et al. 1983), cells of the LAZ-007 line were incubated with eight different organochlorine pesticides. A statistically significant increase in SCE frequency was seen without addition of metabolic activation in cells exposed to 10^{-5} and 10^{-4} M toxaphene, but not at 10^{-6} M. The increases were dose related, but small and did not reach a doubling of the solvent control which is a current criterion for a positive response in an SCE assay. Therefore, the biological significance of this finding is questionable. In the presence of metabolic activation SCE frequency was reduced.

However, in another assay for SCE in Chinese hamster lung cells (DON) (Steinel, et al. 1990) toxaphene was also considered to induce a positive response. In this study, toxaphene statistically increased the frequency of SCE in DON cells in a dose and time dependent manner. Again a doubling over the background rate was not observed, although a close to doubling was seen at the longest incubation time period (28.4 hours). All of the toxaphene doses tested in this study caused cell cycle delay.

Toxaphene has also been reported to induce prophage lambda in *Ercherichia coli*, an assay method that was specifically developed for chlorinated compounds (Houk and DeMarini, 1987). Toxaphene was positive both with and without metabolic activation; however, the response was dramatically reduced in the presence of metabolic activation. Chlordane and dichlorvos were also positive in this assay.

A study by Samosh (1974) reports that accidental exposure of 8 women to toxaphene resulted in an increase in the number of lymphocyte chromosomal aberrations (acentric fragments and chromatid exchanges compared to unexposed individuals). These woman were exposed to an area treated with toxaphene by air.

These results are similar to those that have been reported for phenobarbital (McClain, 1990), a drug that produces a similar tumor pattern and which appears to produce tumors through a similar mode of action. Phenobarbital has given mixed results in an extensive battery of mutagenicity tests. For example, it has been reported both positive and negative for mutagenic effects in the Ames Salmonella assay in strains TA 1535 and TA100. The positive findings were seen only in the absence of metabolic activation. Phenobarbital has been reported to be weakly positive for gene mutations in human lymphoblast cells and both positive and negative in the mouse lymphoma and Chinese hamster V79 cell assays for gene mutations. In the latter assay the positive findings were seen only in the absence of metabolic activation. Results of unscheduled DNA synthesis and DNA binding assays have been negative. Phenobarbital has also been reported to induce SCE in Chinese hamster cells but not to induce SCE in in vivo studies.

Although not strictly a study designed to determine genotoxicity, both phenobarbital (as referenced in McClain, 1990) and toxaphene (Trosko, et al. 1987) have been shown to inhibit cell-to-cell communication. Toxaphene inhibits gap junctional-mediated intercellular communication in Chinese hamster V79 cells in the absence of cytotoxicity. Phenobarbital also inhibits intercellular communication at non-toxic dose levels. For toxaphene, Trosko et al. have concluded that these findings could explain its tumor promoting and neurotoxic effects.

B. Justification for Not Using the Litton Study for Calculating a Cancer Potency Factor

Hercules believes that the toxaphene cancer potency factor should not be calculated based on the liver tumor results in the Litton study. New information available on the NCI mouse oncogenicity study and the use of historical control data provide support for this conclusion. These two factors are discussed in detail below.

1. Results of a Pathology Working Group's Review of the Liver Slides from the NCI Study

Hercules, through an independent contractor, convened a pathology working group[1] (PWG) to review the liver slides from the NCI toxaphene mouse oncogenicity study (1979). The results of this review are tabulated in Table 5 and are appended (Appendix 4).

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[1] The PWG panel members were as follows: Drs. Russell C. Cattley, Michael R. Elwell, Jerry F. Hardisty, Joel R. Leininger, Ernest E. McConnell, and Jerrold M. Ward.

Table 5. Liver Tumor Incidence in the NCI Mouse Study (1979) Determined by the PWG

	Dosage Levels (ppm)			
Tumor Type	**0[a]**	**0[b]**	**99**	**198**
		Males		
Adenoma	2/10	5/48	30/50	42/47[d]
Carcinoma	0/10	3/48	8/50	5/47
Total	2/10	7/48	37/50[c]	45/47
		Females		
Adenoma	0/10	1/50	11/49	37/47
Carcinoma	0/10	0/50	0/49	3/47
Total	0/10	1/50	11/49	39/47

[a] Concurrent Control.

[b] Pooled Control.

[c] The EPL/PWG report indicates 37 animals with carcinoma or adenoma in the individual animals data contrary to the summary table in the report.

[d] The NCI Experimental Design Report states that there were only three "autolysis" animals at the high dose; therefore, there were 47 animals at risk in the high dose group.

A comparison of the PWG findings with those contained in the original study report (Table 5) indicates how significantly diagnostic criteria for liver tumors have changed since the late 1970s. [One member of the PWG (J.M. Ward) was also involved in the original review of the study results by NCI.] Most noteworthy are the PWG's diagnosis of a preponderance of benign tumors (adenomas, frequently designated as neoplastic nodules or carcinomas by the former diagnostic criteria) compared to carcinomas, and a reduction of the total number of tumors in the low-dose group. Furthermore and most importantly, there was no statistically significant increase in carcinomas at any dose level, nor was there a dose-response or sex difference. Thus, toxaphene induced the occurrence of primarily benign liver tumors in mice, and not malignant tumors as originally diagnosed.

Because the diagnostic criteria for liver tumors has changed since the liver slides from this study were originally read, it is not surprising that the tumor incidence data from this study have changed dramatically after reevaluation by the PWG. Unfortunately, slides are not available from the Litton study for reanalysis; however, it is not unreasonable to conclude that the number of adenomas and carcinomas would change dramatically after reanalysis.

2. Historical Control Data and Statistical Significance

Historical control data for spontaneously occurring liver neoplasms in $B6C3F_1$ mice are available from NCI bioassays completed in the 1970s, and are presented in several publications (Haseman et al., 1984; Haseman et al., 1985; Tarone et al., 1981; Ward et al., 1979; Ward, 1983). Historical control data from five separate laboratories contracted by NCI to conduct 24-month bioassays were compared by Tarone et al. (1981). The results indicate that the range for total liver tumors (adenomas/neoplastic nodules plus carcinomas) is 7% to 58% for male $B6C3F_1$ mice, and 0-21% for females.

The incidence of total liver tumors in the Litton toxaphene study, which was also a 24-month bioassay and conducted according to the NCI protocol, was statistically increased ($p<0.05$) at the high-dose level only in male mice compared to concurrent controls. The incidence was 18/53, or 35%, which is well within the historical control range for this tumor type during this time period in this strain of mouse. Although not statistically increased compared to the concurrent controls, the total liver tumor incidence in female mice (11.5%) was also well within the NCI historical control incidence. The use of NCI historical control data for comparison is appropriate because Litton was also an NCI contract laboratory during the time period this study was conducted, and its historical control data from NCI-contracted studies are in the NCI historical control database. Historical control data compiled by Charles River on $B6C3F_1$ mice corroborates the NCI historical control data (Appendix 5). The Charles River historical control incidence for hepatocellular adenomas in male mice ranged from 0-43.3%, and from 0-17.1% for female mice. The incidence of **combined** hepatocellular adenomas and carcinomas in male and female toxaphene-treated mice in the Litton study is well within this range.

In addition, Haseman (1983) questions the biological relevance and relevance to treatment of a statistical increase in a commonly occurring tumor in one sex and one species at the $p<0.05$ level. He believes that in such a case, $p<0.01$ is the appropriate statistical marker for relevance. EPA references Haseman's paper in its proposed 1996 Carcinogen Risk Assessment Guidelines (EPA, 1996a) and concludes, ". . . animal bioassays presenting only one significant result that falls short of the 1% level for a common tumor may be treated with caution," indicating that the Agency also recognizes the questionable biological significance of such a finding.

Thus, the biological significance and relationship to treatment of a statistical increase in commonly occurring tumors in male mice at the $p<0.05$ level that is also within the historical control range is certainly questionable and unlikely to be of any significance to human health.

In summary, Hercules believes that EPA should not use the Litton study for calculating the cancer potency factor for toxaphene for the following reasons.

- Liver tumors were statistically increased only at the high dose and only in male mice in the Litton study.
- The statistical significance of the tumor response at a probability level of 0.05 is of questionable biological significance for a commonly occurring tumor (Haseman, 1983).
- The incidence of liver tumors in male mice was well within the historical control range of NCI studies conducted according to a similar dosing regime and of the same duration (Tarone et al., 1981).
- As demonstrated by the PWG report on the reevaluation of the liver slides from the NCI study, the diagnostic criteria for liver tumors have changed dramatically since the conduct of this study. Therefore, the total number of liver tumors (adenomas and carcinomas) reported in the NCI and Litton study reports is not accurate by today's standards, and this would affect the cancer factor potency calculation.

For the above reasons, Hercules concludes that the results of the Litton study are not suitable for risk assessment purposes because they do not demonstrate unequivocally that toxaphene produced liver tumors in male $B6C3F_1$ mice, and because the liver tumors were not accurately diagnosed by today's criteria.

C. Justification for Using the NCI Study Results

In the NCI study, higher dose levels of toxaphene were tested and the increased incidence of liver tumors in both male and female toxaphene-treated mice was unequivocal. The incidence of combined liver tumors (adenomas and carcinomas) based on the PWG reevaluation was statistically increased in male mice at a probability level of <0.003 or less by the Fisher's exact test when comparing either dose group to the pooled or matched control group (Appendix 4). In female mice, statistical significance for total liver tumors was at a probability level of <0.004 or less when compared to the pooled control data. As noted earlier, there was no increase in malignant tumors in either sex. In addition, as noted above and as found in the PWG review, the liver tumors (males and females) in this study have been reevaluated by a PWG using current diagnostic criteria. Therefore, the tumor incidence data in the NCI study—based on current diagnostic criteria—are much more reliable than the Litton data for cancer potency calculations and are the data used for the recalculation by Hercules.

III. RECALCULATION OF TOXAPHENE CANCER POTENCY FACTOR

According to information contained on IRIS, the Agency used the male liver tumor incidence data from the Litton study to calculate a cancer potency factor (q_1*). Using the linearized multistage procedure and extra risk, the q_1* was calculated to be 1.1 $(mg/kg/day)^{-1}$. Hercules contracted Sielken, Inc. (Sielken) to calculate a q_1* based on the male and female total tumor incidence data from the reevaluated NCI study. Because actual compound intake and food consumption data were not available for this study, the default Lehman conversion factor of 0.15 was used to convert ppm toxaphene in the diet to mg/kg/day. Using this default conversion factor is conservative because actual compound intake frequently is greater in long-term studies in both rats and mice. For example, in one recently conducted 18-month oncogenicity study in $B6C3F_1$ mice, the dose levels in the diet were 100, 800, 8000, and 16,000 ppm. Using Lehman's conversion factor these dose levels convert to 15, 120, 1200, and 2400 mg/kg/day; however, using actual food consumption data, the actual compound intake was 17.4, 143, 1476, and 2978 mg/kg/day for males and 20.8, 167, 1707, and 3448 mg/kg/day for females. This is 20% to 30% higher than would be predicted using the Lehman default conversion factor even without considering the food wastage occurring in mice feeding studies. Food consumption in this recent study was unaffected by treatment, except at the high dose, at which it was decreased.

It is unclear how the Agency converted ppm in the diet to mg/kg/day for the Litton study in calculating the q_1* of 1.1 $(mg/kg/day)^{-1}$ because food consumption data are also not available for this study. It also appears that the Lehman default conversion factor was not used judging from the dosage levels in mg/kg/day used for calculating the q_1*.

Sielken used several different scenarios to calculate q_1* values using the mouse liver tumor data from the PWG report. Hercules considers that the scenarios contained in Table 2 of Sielken's report (Appendix 6) are most relevant and should be used by EPA. The potency factors presented in Table 2 (Appendix 6) were derived using the male and female mouse liver adenoma/carcinoma incidence data. Of the potency factors calculated and presented in this table, Hercules believes that the upper bound potency factors derived using EPA's current standard defaults (extra risk, 60 kg human, 30 g mouse, and an interspecies scaling factor based on the three-fourths power of body weight; EPA personal communication 1997), the time of observation of each mouse, and the conservative low-dose linear extrapolation below the benchmark dose (LED_{10}) are most appropriate for EPA's risk assessment purposes and are supportable under EPA's proposed (EPA 1996a) cancer risk assessment guidelines. The potency factors using the above defaults/adjustments are 0.23 (mg/kg/day)$^{-1}$ using the male mouse adenoma/carcinoma incidence data, and 0.11 (mg/kg/day)$^{-1}$ using the female mouse liver adenoma/carcinoma incidence data. Hercules believes that the geometric mean of these two potency factors [0.16 (mg/kg/day)$^{-1}$] is most appropriate for EPA to use for risk assessments relating to human exposure to toxaphene. Hercules would like to point out from Sielken's analysis that:

- The upper bound q_1* toxaphene would not have changed if it had been based on added risk rather than the EPA default of extra risk.
- The upper bound q_1* for toxaphene would have decreased 600,000-fold—from 0.16 to 2.7 x 10^{-7}—if the slope of the extra risk had been evaluated at 1 x 10^{-6} mg/kg/day rather than being characterized by the slope of a linear extrapolation below the LED_{10}.[2]
- The upper bound q_1* for toxaphene would have decreased 60-fold—from 0.16 to 0.0025—if even a minimal adjustment were made for interspecies differences in the background transition rates from stage to stage in the multistage carcinogenic process.

IV. CONCLUSIONS

Hercules believes that the liver tumor data from the NCI mouse oncogenicity study on toxaphene are more appropriate for calculating the toxaphene cancer potency factor than the data from the Litton study. Furthermore, Hercules believes that the potency factor [0.16 (mg/kg/day)$^{-1}$] calculated by Sielken using the male and female mouse liver adenoma/carcinoma data should be used for regulatory and risk assessment purposes by EPA. Hercules, therefore, requests that EPA consider the rationale presented here and make the scientifically justifiable and appropriate changes in its position on the toxaphene cancer potency factor, including the adoption of a cancer potency factor of 0.16 (mg/kg/day)$^{-1}$.

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[2] Selection and derivation of LED_{10}s are discussed in Appendices 6 and 7.

TOXAPHENE:
BASIS FOR A CHANGE IN AND RECALCULATION OF THE CANCER POTENCY FACTOR

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APPENDIX 1

INVESTIGATION OF HEPATIC CYTOCHROME P450 ENZYME INDUCTION AND DNA ADDUCT FORMATION IN MALE CD1 MICE FOLLOWING ORAL ADMINISTRATION OF TOXAPHENE

INVESTIGATION OF HEPATIC CYTOCHROME P450 ENZYME INDUCTION AND DNA ADDUCT FORMATION IN MALE CD1 MICE FOLLOWING ORAL ADMINISTRATION OF TOXAPHENE.

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Although it has previously been established that exposure to Toxaphene induces hepatic cytochrome P450 in rodents and induces liver tumors in mice following chronic exposure, the mechanism of carcinogenicity has yet to be elucidated. Peroxisomal proliferation has frequently been evoked as a nongenotoxic mechanism of hepatocarcinogenesis. Since all peroxisomal proliferators studied to date induce cytochrome P450 4A1, the aim of these studies was to determine whether induction of cytochrome P450 4A1 is specifically associated with the Toxaphene-induced increase in hepatic P450. In addition, we also measured Toxaphene-induced hepatic DNA adduct levels in order to evaluate whether DNA binding is involved in toxicity.

Groups of three or four male CD1 mice were treated by oral intubation with corn oil vehicle or 10, 25, 50 or 100 mg/kg of Toxaphene in vehicle for seven consecutive days and sacrificed 24 hours following the last treatment. The physical condition and weight of the animals were observed daily. The livers from two individual animals per group were pooled and microsomal fractions subsequently prepared. Total cytochrome P450 and cytochrome b5 levels were measured by difference spectroscopy according to the method of Omura and Sato (1964). Induction of CYP 4A1 was evaluated by measuring the levels of immunodetectable microsomal protein using Western blot analysis. DNA was isolated from previously frozen 100 mg samples of liver tissue using phenol/chloroform extraction. DNA adduct levels were analyzed using nuclease P1-enhanced DNA

[^{32}P]postlabeling method (Reddy and Randerath, 1986).

In comparison to control mice, significant increases in liver weight and liver /body weight ratios were observed in mice treated with 50 mg/kg and 100 mg/kg of Toxaphene. Toxaphene caused a dose dependent increase in total cytochrome P450 levels to a maximum of 1.6X the control level with similar increases in hepatic microsomal cytochrome b5 levels. This effect of Toxaphene on total hepatic P450 levels is consistent with previous reports. No increases in the levels of immunodetectable CYP 4A1 were detected by Western blot analysis of liver microsomal proteins from Toxaphene treated mice. In contrast, immunodetectable levels of CYP 4A1were significantly increased in liver microsomal proteins from mice treated orally for three consecutive days with 200 mg/kg of clofibrate, a known peroxisomal proliferator. These findings suggest that Toxaphene - induced hepatic CYP 450 induction does not involve CYP 4A1 and that peroxisomal proliferation may not play a role in toxicity. Significant increases in immunodetectable levels of CYP 2B were, however, observed in Toxaphene treated mice. This finding is indeed consistent with earlier reports demonstrating that Toxaphene and other pesticides induce the phenobarbital -inducible subfamily of cytochromes P450. Preliminary analysis of hepatic DNA adduct levels in these mice by nuclease P1-enhanced DNA [^{32}P]postlabeling showed no evidence of DNA adduct formation, suggesting either that adducts are not formed under these conditions, are formed but ar rapidly repaired, or are formed below the limits of detection.

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HYPOTHESIS: THE MECHANISM OF TOXAPHENE - INDUCED CYTOCHROME P450 ENZYME INDUCTION IS SPECIFICALLY ASSOCIATED WITH CYP4A1, AN ISOZYME OF CYTOCHROME P450 THAT HAS CONSISTENTLY BEEN SHOWN TO BE INDUCED BY COMPOUNDS THAT CAUSE PEROXISOMAL PROLIFERATION.

EXPERIMENTAL APPROACH:

1. TREAT ANIMALS TO INDUCE MICROSOMAL ENZYMES
2. SACRIFICE ANIMALS AND PREPARE MICROSOMES
3. MEASURE LEVELS OF TOTAL MICROSOMAL PROTEIN, CYTOCHROME P450 AND CYTOCHROME B5
4. DETERMINE WHETHER LIVER MICROSOMAL CYP 4A1 INCREASED BY WESTERN BLOT ANALYSIS.
5. IF CYP4A1 IS INCREASED CARRY OUT NORTHERN BLOT ANALYSIS OF HEPATIC RNA TO DETERMINE IF CYP 4A1 ASSOCIATED mRNA LEVELS ARE INCREASED AND ASSAY THE LEVELS OF CYP 4A1 ASSOCIATED CATALYTIC ACTIVITY, LAURIC ACID HYDROXYLATION.

EFFECT OF TOXAPHENE AND CLOFIBRATE TREATMENT ON BODY WEIGHT GAIN, LIVER WEIGHT, AND LIVER/BODY WEIGHT RATIOS IN MALE CD/1 MICE

TREATMENT	BODY WEIGHT/ DAY 1	BODY WEIGHT/ DAY 8	LIVER WEIGHT	LIVER/BODY WEIGHT x 100
CORN OIL CONTROL	26.0 ± 0.71	29.5 ± 0.58	1.67 ±0.14	5.66 ± 0.37
TOXAPHENE 10MG/KG	25.4 ± 1.02	28.3 ± 1.71	1.81 ± 0.33	6.35 ± 0.84
TOXAPHENE 25MG/KG	26.0 ± 0.71	28.9 ± 1.26	1.84 ± 0.32	6.41 ± 1.05
TOXAPHENE 50 MG/KG	25.0 ± 1.41	28.3 ± 0.96	2.38 ± 0.31*	8.39 ± 0.86*
TOXAPHENE 100 MG/KG	25.5 ± 1.34	28.3 ± 1.53	2.86 ± 0.37*	10.08 ± 0.77*
CLOFIBRATE 200 MG/KG	24.8 ± 1.48	28.5 ± 1.29	1.61 ± 0.20	5.64 ± 0.54

ANIMALS WERE TREATED BY ORAL INTUBATION ONCE A DAY FOR 7 CONSECUTIVE DAYS AND WERE SACRIFICED 24 HOURS FOLLOWING THE FINAL TREATMENT.

DATA REPRESENT THE MEAN ± THE STANDARD DEVIATION OF 3 ANIMALS PER GROUP (TOXAPHENE 100 MG/KG) OR 4 ANIMALS PER GROUP (ALL OTHERS).
* statistically significant from control and all other treament groups at $p<0.05$

TOXAPHENE TENDED TO INCREASE ANIMAL LIVER WEIGHT AND LIVER/BODY WEIGHT RATIOS. STATISTICALLY SIGNIFICANT DIFFERENCES WERE OBSERVED AT THE 50 AND 100 MG/KG DOSES.

EFFECT OF TOXAPHENE ON TOTAL CYTOCHROME P450 AND CYTOCHROME B5 ACTIVITY

TREATMENT	PROTEIN MG/ML	CYTOCHROME P450 NMOLES/MG PROTEIN	CYTOCHROME B5 NMOLES/MG PROTEIN
CORN OIL CONTROL	16.9 (15.7-18.1)	1.11 (1.09-1.12)	0.384 (0.379-0.389)
TOXAPHENE 10MG/KG	21.8 (18.3-25.2)	1.29 (1.28-1.30)	0.45 (0.431-0.468)
TOXAPHENE 25 MG/KG	25.7 (23.5-27.9)	1.16 (0.99-1.32)	0.383 (0.328-0.438)
TOXAPHENE 50 MG/KG	31.0 (30.2-31.8)	1.55 (1.32-1.78)	0.55 (0.454-0.646)
TOXAPHENE 100 MG/KG	31.4 (27.4-31.4)	1.65 (1.52-1.77)	0.618 (0.542-0.694)
CLOFIBRATE 200 MG/KG	16.8 (15.8-17.8	0.89 (0.72-1.06)	0.398 (0.385-0.41)

DATA REPRESENT THE MEAN OF 2 INDIVIDUAL SAMPLES FOR EACH TREATMENT. NUMBERS IN THE PARENTHESES ARE THE VALUES FROM EACH INDIVIDUAL SAMPLE.
EACH SAMPLE REPRESENTS THE LIVER MICROSOMAL FRACTION FROM POOL OF 2 INDIVIDUAL ANIMALS WITH THE EXCEPTION OF THE TOXAPHENE 100 MG/KG GROUP WHERE ONE SAMPLE WAS A POOL OF 2 AND THE OTHER WAS AN INDIVIDUAL LIVER.

TOXAPHENE TREATMENT TENDED TO INCREASE TOTAL P450 LEVELS TO A MAXIMUM OF APPROXIMATELY 1.6X THE CONTROL LEVEL AT THE HIGHEST DOSE OF TOXAPHENE. TOXPAHENE ALSO INCREASED CYTOCHROME B5 LEVELS. CLOFIBRATE TREATMENT (THE POSITIVE CONTROL) DID NOT EFFECT TOTAL P450 AND CYTOCHROME B5 LEVELS.

HYPOTHESIS: HEPATIC DNA ADDUCTS WILL BE DETECTABLE IN MICE TREATED WITH TOXAPHENE.

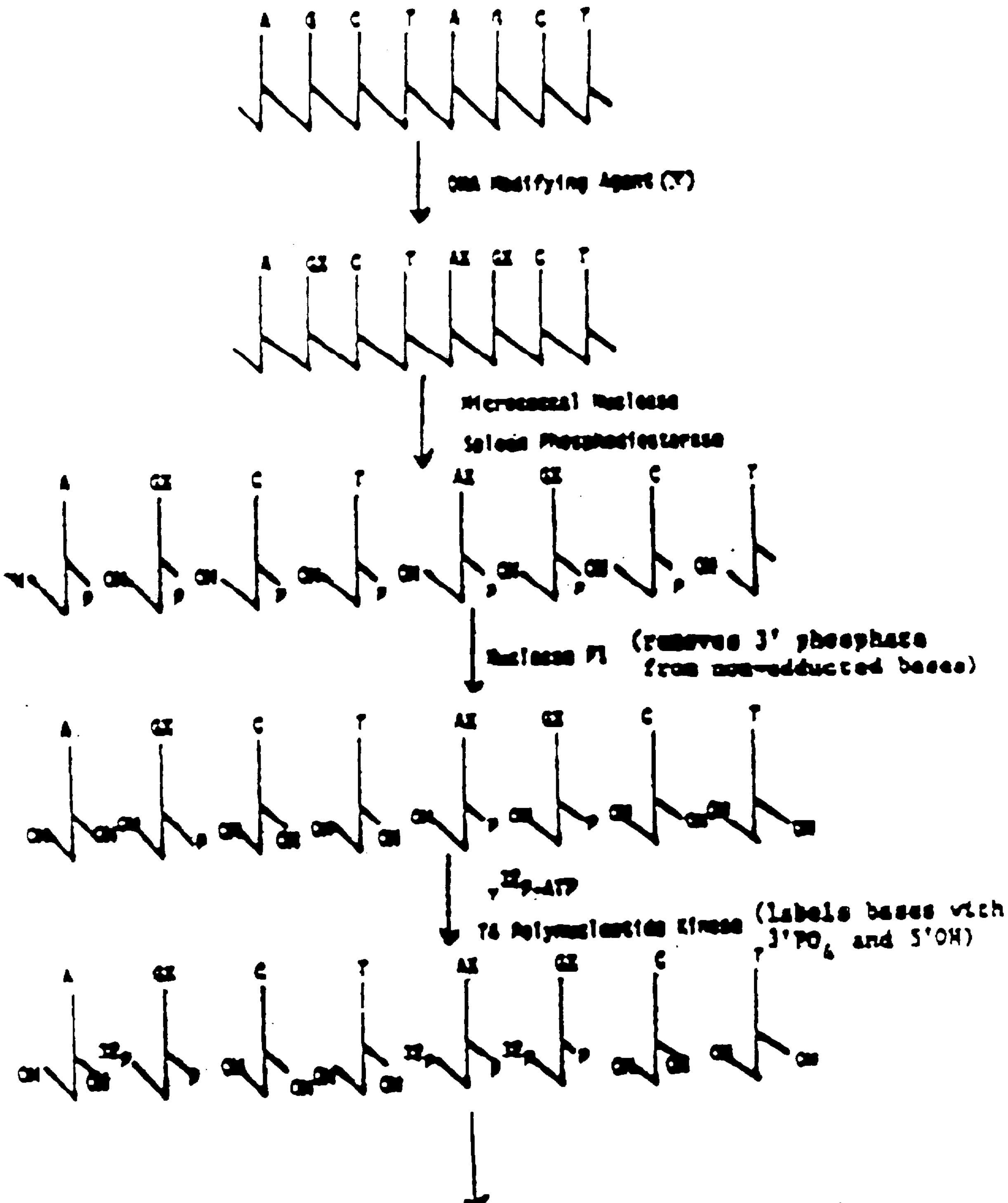
EXPERIMENTAL APPROACH:

1. TREAT ANIMALS WITH TOXAPHENE AND ISOLATE LIVER DNA BY PHENOL/CHLOROFORM EXTRACTION.

2. MEASURE DNA ADDUCT LEVELS BY THE NUCLEASE P1 ENHANCED [^{32}P]POSTLABELING METHOD.

Outline of DNA $[^{32}P]$postlabeling method.

Modified from Haseltine, W., Franklin, W. and Lippke, J. Environmental Health Perspectives 48: 29-41, 1983.


A G C T A A C T
DNA Modifying Agent (X)
A GX C T AX GX C T
Micrococcal Nuclease
Spleen Phosphodiesterase
A GX C T AX GX C T
OH p
Nuclease P1 (removes 3' phosphate from non-adducted bases)
A GX C T AX GX C T
OH p
γ 32P-ATP
T4 Polynucleotide Kinase (labels bases with 3'PO4 and 5'OH)
A GX C T AX GX C T
OH 32P p

^{32}P Labeled bases are separated by chromatography using PEI-cellulose plates or C18 reversed phase tlc. Autoradiograms are made of the plates and the density of spots determined with a densitometer or spots are excised from plates and counted.

APPENDIX 2

IMMUNOHISTOCHEMICAL EVALUATION OF ALPHA$_{2u}$-GLOBULIN IN KIDNEYS OF RATS EXPOSED TO TOXAPHENE FOR 28 DAYS

IMMUNOHISTOCHEMICAL EVALUATION OF ALPHA$_{2U}$-GLOBULIN IN KIDNEYS OF RATS EXPOSED TO TOXAPHENE FOR 28 DAYS

HWA PROJECT NUMBER 116-193
EPL PROJECT NUMBER 172-003

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JUNE 20, 1995

James A. Swenberg

Introduction

Alpha$_{2U}$-globulin nephropathy is a well characterized toxicity of male rats that results in the accumulation of hyalin droplets in the proximal tubule of the kidney, the formation of granular casts at the junction of the thin loop of Henle, and on chronic exposure, linear mineralization of the renal medulla and the formation of renal neoplasia (1,2). Alpha$_{2U}$-globulin is a low molecular weight protein (18,700 kd) that is synthesized in the liver of male rats under androgenic control, secreted into the blood, is filtered freely by the renal glomerulus, and is resorbed by the P_2 segment of the proximal tubule. A variety of chemicals, such as d-limonene, or their metabolites have been shown to reversibly bind to alpha$_{2U}$-globulin, causing a decrease in the digestibility of the protein-chemical complex in renal lysosomes. This leads to an accumulation of the protein-chemical complex in the P_2 segment of the proximal tubule of the kidney (3-6). This toxicity only occurs in male rats of strains that synthesize alpha$_{2U}$-globulin and not in other species, including humans (7-9). A thorough review of alpha$_{2U}$-globulin nephropathy by the U.S. Environmental Protection Agency concluded that alpha$_{2U}$-globulin nephropathy should not be used for the purposes of human risk assessment (10).

The renal toxicity of Toxaphene was evaluated in rats in a 28-day dietary study (11). The study found an increase in hyalin droplet nephropathy that was characterized by an accumulation of hyalin droplets in the cytoplasm of the proximal convoluted tubules, granular casts, and degeneration and regeneration of the epithelial cells in the proximal convoluted tubules. A similar type of nephropathy was not seen in the kidneys of female rats. Paraffin sections of male rat kidneys were stained immuno-histochemically for this protein using a monoclonal antibody against alpha$_{2U}$-globulin. These sections were examined histopathologically for evidence of alpha$_{2U}$-globulin nephropathy.

Materials and Methods

Paraffin tissue sections from 10 male rat kidneys from the control and dosed groups of the 28-day study (11) were received on Fisher $^+$ treated slides, deparaffinized and rehydrated through graded alcohols to phosphate buffered saline (PBS) containing 1% Tween 20 (Fisher Scientific). Positive control kidney sections from male Sprague Dawley rats gavaged with d-Limonene (150 mg/kg/day, 4 days) at the University of North Carolina were included with each set of slides to be processed. Sections were pretreated with Target Unmasking Fluid (TUF, Signet Laboratories). Briefly, tissue sections were placed in plastic coplin jars, immersed in TUF and microwaved for 7.5 minutes, allowed to cool to room temperature and then rinsed with distilled deionized water. Sections were then incubated at 37 °C for 20 minutes in 4N HCl, rinsed with distilled deionized water and rinsed with two changes of PBS for 5 minutes each. The sections were transferred to a humidified staining chamber where all subsequent steps were done at room temperature and in-between each step the sections were rinsed twice with PBS containing 1% Tween 20 (PBSt) 5 minutes each rinse. Endogenous peroxidase activity was blocked with 0.03% hydrogen peroxide. Anti-alpha$_{2U}$-globulin monoclonal antibodies were dispensed (dilution 1:100,000; proprietary antibody, J.A. Swenberg) and the sections incubated for 10 minutes. A secondary antibody (anti mouse/ anti rabbit) which is preconjugated with a Horse Radish Peroxidase (HRP) labeled polymer (Dako Corp.) was applied to the sections for 15 minutes. The HRP label was visualized with 3,3'-diaminobenzidine chromogen which was applied for 8 minutes. This was followed by the counter stain, Mayer's Hematoxylin (Sigma Chemical) for 5 minutes. Specimens were removed from the incubation chamber, dehydrated through graded alcohols, cleared with an aliphatic hydrocarbon (Clear-Rite 3, Richard-Allan Med. Ind.) and coverslipped with Permount (Fisher Scientific).

Results

The results of alpha$_{2U}$-globulin immunohistochemistry showed positive staining for all male rats. The amount and type of staining was, however, different between the Toxaphene-treated and control rats (Table 1). Of the 9 controls that had evaluable slides, 5 showed slight immunostaining of small droplets in the same areas that had small Mallory-Heidenhain-positive protein droplets, and 3 exhibited moderate immunostaining of more numerous small and large droplets. Prominent numbers of large droplets staining positively for alpha$_{2U}$-globulin were present in 7 of the 10 slides from the Toxaphene-exposed rats and 3 additional cases were similar to the moderately positive staining control rats. In addition to the increased staining of droplets in the proximal convoluted tubules, 4 of the Toxaphene-exposed rats had granular casts identified at the junction of the inner and outer stripe of the medulla and these also stained weakly positive for alpha$_{2U}$-globulin. The d-limonene positive control slides consistently exhibited increased specific staining of lysosomes for alpha$_{2U}$-globulin and the negative control slides were always negative.

Discussion

The presence of an increased number and size of hyalin droplets that stain positively for alpha$_{2U}$-globulin and the characteristic granular casts at the junction of the inner and outer stripe of the medulla provide strong evidence for the induction of alpha$_{2U}$-globulin nephropathy by Toxaphene. The granular casts represent accumulations of dead P_2 renal epithelial cells that contain alpha$_{2U}$-globulin. It is actually somewhat unusual to find this lesion in studies of this short of a duration. Typically, the granular casts are found in studies of 3-12 months exposure. Alpha$_{2U}$-globulin nephropathy is a well characterized disease that is specific for male rats. A thorough review of alpha$_{2U}$-globulin nephropathy by the U.S. Environmental Protection Agency concluded that alpha$_{2U}$-globulin nephropathy should not be used for the purposes of human risk assessment (10).

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Table 1. Alpha$_{2U}$-globulin Immunohistochemistry of Control and Toxaphene-exposed Male Rat Kidneys.

Animal Number	Group	Alpha$_{2U}$-globulin Immunohistochemistry
B52638/P67385	Control	Slight staining of proximal tubules
B52639/P67386	Control	Slight staining of proximal tubules
B52640/P67387	Control	Slight staining of proximal tubules
B52641/P67388	Control	Moderate staining of proximal tubules
B52642/P67389	Control	Slight staining of proximal tubules
B52643/P67390	Control	Slight staining of proximal tubules
B52644/P67391	Control	Slight staining of proximal tubules
B52645/P67392	Control	Moderate staining of proximal tubules
B52646/P67393	Control	No slide available
B52647/P67394	Control	Slight staining of proximal tubules
B52658/P67395	Toxaphene	Moderate staining of proximal tubules
B52659/P67396	Toxaphene	Moderate staining of proximal tubules
B52660/P67397	Toxaphene	Prominent staining of proximal tubules and granular casts
B52661/P67398	Toxaphene	Prominent staining of proximal tubules
B52662/P67399	Toxaphene	Prominent staining of proximal tubules
B52663/P67400	Toxaphene	Prominent staining of proximal tubules and granular casts
B52664/P67401	Toxaphene	Moderate staining of proximal tubules
B52665/P67402	Toxaphene	Prominent staining of proximal tubules and granular casts
B52666/P67403	Toxaphene	Prominent staining of proximal tubules
B52667/P67404	Toxaphene	Prominent staining of proximal tubules and granular casts

APPENDIX 3

ATSDR PROFILES: TOXAPHENE

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TOXAPHENE

Draft for Public Comment
(Update)
Comment Period Ends: February 21, 1995

Prepared by:

Research Triangle Institute
Under Contract No. 205-93-0606

Prepared for:

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

August 1994

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The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles contact ATSDR at:

Agency for Toxic Substances and Disease Registry

Division of Toxicology/Toxicology Information Branch

1600 Clifton Road NE, E-29

Atlanta, Georgia 30333

FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The availability of the revised priority list of 275 hazardous substances was announced in the Federal Register on February 28, 1994 (59 FR 9486). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); and October 28, 1992 (57 FR 48801).

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following:

(A) The examination, summary, and interpretation of available toxicological information and epidemiological evaluations on a hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects.

(C) Where appropriate, identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile is intended to succinctly characterize the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented, but described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

Each toxicological profile begins with a public health statement, that describes in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protect public health will be identified by ATSDR and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

The principal audiences for the toxicological profiles are health professionals at the federal, state, and local levels, interested private sector organizations and groups, and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Comments should be sent to:

Agency for Toxic Substances and Disease Registry

Division of Toxicology

Mail Stop E-29

Atlanta, Georgia 30333

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention (CDC), and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

David Satcher, M.D., Ph.D.
Administrator
Agency for Toxic Substances and Disease Registry

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the consistency with ATSDR policy.

2. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying endpoints.

3. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

4. Quality Assurance Review. The Quality Assurance Branch assures that consistency across profiles is maintained, identifies any significant problems in format or content, and establishes that Guidance has been followed.

PEER REVIEW

A peer review panel was assembled for toxaphene. The panel consisted of the following members:

1. Dr. William Buck, Private Consultant, Consul-Tox, Inc., Tolono, Illinois.

2. Dr. Anthony Donigan Jr., Private Consultant, AQUA-TERRA Consultant, Mountain View, California.

3. Dr. Donald Morgan, Private Consultant, Iowa City, Iowa.

These experts collectively have knowledge of toxaphene's physical and chemical properties, toxico-kinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about toxaphene and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,430 hazardous waste sites as the most serious in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal clean-up activities. Toxaphene has been found in at least 58 of the sites on the NPL. However, the number of NPL sites evaluated for toxaphene is not known. As EPA evaluates more sites, the number of sites at which toxaphene is found may increase. This information is important because exposure to toxaphene may cause harmful health effects and because these sites are potential or actual sources of human exposure to toxaphene.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking substances containing the substance or by skin contact with it.

If you are exposed to a substance such as toxaphene, many factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, gender, nutritional status, family traits, life-style, and state of health.

1.1 WHAT IS TOXAPHENE?

Toxaphene, also known as campheclor, chlorocamphene, polychlorocamphene, and chlorinated camphene, is a manufactured insecticide containing over 670 chemicals. Toxaphene is usually found as a solid or gas. In its original form, toxaphene is a yellow to amber waxy solid that smells like turpentine. It does not burn and evaporates when in solid form or when mixed with liquids. Toxaphene was one of the most heavily used insecticides in the United States until 1982. Toxaphene was used primarily in the southern United States to control insect pests on cotton and other crops. It was also used to control insect pests on livestock and to kill unwanted fish in lakes. In 1990, the EPA banned all uses of toxaphene in the United States or any of its territories because of scientific evidence that it harms human and animal health. In 1993, the EPA banned the importation of food containing toxaphene residues into the United States or any of its territories.

1.2 WHAT HAPPENS TO TOXAPHENE WHEN IT ENTERS THE ENVIRONMENT?

Toxaphene enters the environment after it is applied to a crop or poured into a lake. Toxaphene can enter the air (by evaporation), the soil (by sticking to soil particles), and the water (from runoff after rains). Toxaphene may also enter the environment from hazardous waste sites or when it accidentally spills or leaks during storage or transport. It does not dissolve well in water, so it is more likely to be found in air, soil, or the sediment at the bottom of lakes and streams. If toxaphene is found in surface water or groundwater, it is usually at very low levels. Once toxaphene is in the environment, it can last for years because its breakdown is very slow. This means there is still the chance of being exposed to toxaphene in the United States even though it has not been widely used for over 10 years. Because toxaphene breaks down slowly, exposure will probably be to the original material. For more information on the chemical and physical properties of toxaphene, refer to Chapter 3.

Levels may be high in some predatory fish and mammals because toxaphene accumulates in fatty tissues. For example, when a raccoon eats a contaminated fish, some of the toxaphene in the fish is transferred to the raccoon. The more contaminated fish the raccoon eats, the more toxaphene it acquires. This means that even when toxaphene levels are low or confined to a certain area, they could be high in individual animals. Care should be taken when hunting or fishing in areas contaminated with toxaphene. For more information on toxaphene in the environment, see Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO TOXAPHENE?

Since the use of toxaphene is banned in the United States, you can probably only be exposed to it in areas where it is concentrated (such as a waste site). In those areas, there is a greater chance of breathing or directly contacting the chemical. People may also be exposed to toxaphene by eating contaminated soil. Infants and toddlers have the greatest risk because they are likely to put things in their mouths. People who eat large quantities of fish and shellfish in areas contaminated by toxaphene may also have more risk because those animals tend to concentrate toxaphene in their fatty tissues. You can also be exposed to toxaphene by breathing contaminated air, but concentrations in outdoor air are very low so you are not likely to be exposed to unhealthy levels in air. For more information on human exposure to toxaphene, see Chapter 5.

1.4 HOW CAN TOXAPHENE ENTER AND LEAVE MY BODY?

Toxaphene can enter the body through eating contaminated food or soil, through the skin after direct contact with contaminated substances, and through the lungs after breathing its vapors. Once toxaphene enters the body, it rapidly spreads to all organs. Toxaphene is quickly broken down in the body and excreted in urine and feces. Nearly all (approximately 90%) the toxaphene is eliminated from the body within 24-36 hours after absorption. However, studies in animals show that low levels of toxaphene may remain in fat for months. It is not clear how this can affect human health. Chapter 2 contains more detailed information on how toxaphene enters and leaves the body.

1.5 HOW CAN TOXAPHENE AFFECT MY HEALTH?

Breathing, eating, or drinking high levels of toxaphene has been reported to damage the lungs, nervous system, liver, and kidneys, and can cause death. Of course, how severe the effects are depends on how much toxaphene is absorbed. Because toxaphene is no longer widely used, the chances of high-level exposure are small. If exposure occurs, it is likely to be at a low level and probably over a long time (that is, more than 1 year). Scientists have no information about how low-level exposure for a long time affects humans; however, animal studies have been conducted to try to answer that question.

Studies in animals show that long-term exposure (1-2 years) to toxaphene can damage the liver, kidneys, adrenal gland, and immune system, and may cause minor changes in fetal development. Toxaphene may also cause cancer in laboratory animals. The results of studies where animals were exposed to relatively high levels of toxaphene for most of their lives show that the thyroid gland in some of the animals developed cancerous cell types. The EPA has determined that toxaphene is a probable human carcinogen. It should be noted, however, that the average person will never be exposed to toxaphene for a long time (more than 1 year), and not everyone exposed to it will develop cancer. In fact, there is presently no evidence that toxaphene has caused cancer in human beings. See Chapter 2 for more information on toxaphene and cancer.

1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO TOXAPHENE?

Toxaphene and its breakdown products can be detected in blood, urine, breast milk, and body tissues. Because samples are easy to take, urine and blood tests are the most common way to tell if a person has been exposed to toxaphene. Neither of these tests is routinely available at a doctor's office because special equipment is needed to detect toxaphene, but your doctor can send samples to a special laboratory that performs those tests. The tests cannot determine how much toxaphene you have been exposed to. Toxaphene leaves the body quickly, so the tests can only detect it within several days after exposure. Also, if you are exposed to other chemicals at the same time, the test results could be misinterpreted.

Blood and urine tests can confirm that a person has been exposed to toxaphene, but these tests cannot yet predict the kind or severity of any health effects that might occur. See Chapters 2 and 6 for specific information about the tests used to detect toxaphene in the body.

1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government has developed regulatory standards and guidelines to protect individuals from the potential health effects of toxaphene in drinking water and food. The Environmental Protection Agency (EPA) concludes that the amount of toxaphene in drinking water should not exceed 0.005 parts of toxaphene per million parts (ppm) of water and that any release to the environment greater than one pound should be reported. The EPA has also established limits on how much toxaphene can be released from a factory into waste water. The limit is set at 0-1.5 mg of toxaphene per liter (approximately a quart) of water. The EPA has determined that toxaphene is a "hazardous air pollutant" under the Clean Air Act, but the agency has not yet established standards for it. For short-term exposures, EPA concludes that drinking water levels should not exceed 0.5 ppm for 1 day or 0.04 ppm for 10 days. The Food and Drug Administration has set a limit of 6 ppm of toxaphene in crude soybean oil, and EPA has set limits that range from 0.1 to 7 ppm for other raw agricultural products such as sunflower seeds, soybeans, grains, cottonseed, vegetables and fruits (including bananas and pineapples). The EPA has banned the importation of all food containing toxaphene residues and toxaphene can no longer be used in the United States or its territories, so the likelihood of eating contaminated food is small.

The Occupational Safety and Health Administration (OSHA) has set a legally enforceable limit (permissible exposure limit or PEL) of 0.5 milligrams of toxaphene per cubic meter of air in workroom air to protect workers during an 8-hour shift over a 40-hour workweek. For more information on criteria and standards for toxaphene exposure, see Chapter 7.

1.8 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333
(404) 639-6000

This agency can also provide you with information on the location of occupational and environmental health clinics. These clinics specialize in the recognition, evaluation, and treatment of illness resulting from exposure to hazardous substances.

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of toxaphene. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

Toxaphene is a manufactured pesticide that is composed of over 670 different constituents; the relative proportions of the major components of the pesticide are essentially the same in different formulations. The use of toxaphene has been banned in the United States and all of its territories since 1990 (EPA 1990b). Moreover, toxaphene residues are not allowed on any food imported to the United States (EPA 1993b). Nevertheless, because of its widespread use, persistence in the environment, and storage in waste sites, exposure to toxaphene is still possible.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal; and then by health effect--death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects, These data are discussed in terms of three exposure periods--acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures, The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the LSE tables and figures may differ depending on the user's perspective. Public health officials and others concerned with depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of toxaphene are indicated in Table 2-1 and Figure 2-1. Because cancer effects could occur at lower exposure levels, Figure 2-1 also show a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 (10^{-4} to 10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for toxaphene. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix A). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

Very little information is available regarding the health effects of toxaphene following inhalation exposure in humans. Most of the existing data come from case reports and long-term studies of pesticide workers and are of limited value. In such studies, precise levels of exposure are usually not provided, and concurrent exposure to several pesticides confounds the interpretation of the results.

2.2.1.1 Death

No studies were located regarding death in humans or animals following inhalation exposure to toxaphene

2.2.1.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, endocrine, dermal, or ocular effects in humans or animals following inhalation exposure to toxaphene.

One controlled human study was found that investigated the general effects of inhaled toxaphene. Keplinger (1963) reported that no toxic effects were seen in 25 humans exposed to an aerosol containing a maximum of (500mg/m^3) 30 minutes daily for 10 days. The author calculated the exposure dose to be as much as 60 mg per person per day. After a 3-week period, these same subjects were exposed for 3 more 30-minute periods. Examination of these subjects before and after exposures by a dermatologist and an internist (some of them using blood tests and urinalysis) indicated no effects. Due to the limited information reported in this study and the unusual exposure conditions, it is difficult to assess the adequacy of these data. Nevertheless, the study is referenced below for the appropriate systemic endpoints.

Respiratory Effects. Inhaled toxaphene has been reported to cause reversible respiratory toxicity. In two cases, men involved in the spraying of toxaphene (formulated as 60% toxaphene, 35% kerosene, 3% xylol, and 2% emulsifier) for approximately 2 months suffered from acute pulmonary insufficiency (Warraki 1963). Chest x-rays revealed extensive miliary shadows, with one man exhibiting marked bilateral hilar lymphadenopathy. Other clinical findings included elevated sedimentation rates, the presence of blood eosinophilia, and high serum globulin. The diagnosis in both cases was extensive bilateral allergic bronchopneumonia as a result of insecticide exposure. Both patients recovered quickly and completely with cortisone, streptomycin, and isoniazid treatment. Although the clinical sequelae observed in these two patients could be associated with toxaphene exposure, the effects could have been caused by other components of the spray.

No studies were located regarding respiratory effects in animals following inhalation exposure to toxaphene.

Hematological Effects. Blood tests conducted on humans exposed to a toxaphene spray indicated that the pesticide did not cause blood abnormalities (Keplinger 1963). However, the exact dose to which the subjects were exposed could not be determined.

No primary source studies were located that described adverse hematological effects in animals following inhalation exposure to toxaphene. However, no toxaphene-related hematological effects were noted in animals exposed to toxaphene dust or mist (unpublished observations 1955, 1964, 1965, as cited in Boots Hercules Agrochemicals n.d.). These data are limited because only summaries of unpublished data cited in a secondary unpublished bulletin were available for review, thus precluding an assessment of their adequacy.

Hepatic Effects. No studies were located regarding hepatic effects in humans following inhalation exposure to toxaphene.

Slight hepatocellular necrosis was observed in some female rats that survived inhalation exposure to 0.004, 0.012, or 0.04 mg/L (4, 12, or 40 mg/m^3) toxaphene dust for 3 months (unpublished observations as cited in Boots Hercules Agrochemicals n.d.). These data are limited because only summaries of unpublished data cited in a secondary unpublished bulletin were available for review, thus precluding an assessment of their adequacy.

Renal Effects. Urinalysis results from humans exposed to a toxaphene spray indicated that the pesticide did not affect kidney function (Keplinger 1963). However, the actual dose to which the subjects were exposed could not be determined. No animal studies describing toxaphene-related renal toxicity following inhalation exposure were found.

Body Weight Effects. No studies were located regarding body weight effects in humans following inhalation exposure to toxaphene.

In rats, acute exposure to toxaphene decreased body weight; intermediate exposure to toxaphene in rats, guinea pigs, and dogs has also been shown to decrease body weight (unpublished observations, as cited in Boots Hercules Agrochemicals n.d.). These data are limited because only summaries of unpublished data cited in a secondary unpublished bulletin were available for review, thus precluding an assessment of their adequacy.

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals following inhalation exposure to toxaphene.

2.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans following inhalation exposure to toxaphene.

Dogs, rats, guinea pigs, and rabbits exposed to an aerosol of toxaphene dust (5 mg/L, 15% respirable or 750 mg/m^3) for 6 hours per day, 5 days per week for 1 week experienced hyperactivity, tremors, salivation, lacrimation, and tonic-clonic convulsions (Industrial BioTest 1964). It should be noted that some studies conducted by Industrial Biotest have been shown to be less than reliable.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following inhalation exposure to toxaphene.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following inhalation exposure to toxaphene.

2.2.1.7 Genotoxic Effects

A higher incidence of chromosomal aberrations was observed in cultured lymphocytes taken from the blood of eight women exposed to toxaphene than in lymphocytes taken from unexposed women (Samosh 1974). The exposed women had entered a field that had recently been sprayed with toxaphene and were described as presenting "mild to moderate" clinical symptoms. The nature of the symptoms was not reported by Samosh. The women were likely to have been exposed by both the inhalation and dermal routes. The degree of exposure was not known. It is unclear whether the chromosomal aberrations observed in the lymphocytes of these women were directly attributable to the toxaphene exposure.

No studies were located regarding the genotoxic effects in animals following inhalation exposure to toxaphene.

Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding cancer effects in humans or animals following inhalation exposure to toxaphene.

2.2.2 Oral Exposure

Toxaphene is toxic following short-term, high-dose oral exposure. Several cases of fatal and nonfatal poisoning have been reported in humans following the accidental or intentional ingestion of toxaphene or food contaminated with large amounts (gram quantities) of toxaphene. In such instances of acute poisoning, toxaphene stimulates the central nervous system like other chlorinated hydrocarbon pesticides. Long-term studies using high doses indicate that toxaphene causes central nervous system toxicosis and hepatic hypertrophy accompanied by increased microsomal enzyme activity and histological changes in liver cells. The kidneys, spleen, and adrenal gland have also been identified as target organs of toxaphene-induced toxicity.

2.2.2.1 Death

Ingestion of high doses of toxaphene by humans can be fatal. Six cases of acute poisoning were reported, three of which (all children) were fatal (McGee et al. 1952). In all cases, an unknown quantity of toxaphene was ingested, either alone or as a residue of spray on food. Symptoms were usually abruptly manifested by 7 hours post-ingestion and consisted of intermittent convulsions, generally without abdominal pain, vomiting, or diarrhea. Death was attributed to respiratory failure resulting from the seizures. It is estimated that the approximate minimum lethal dose in humans is 2-7 g (Hayes 1963); however, the data used to calculate that dose range was not presented.

The oral LD$_{50}$s obtained in laboratory animals can vary according to species, solvent used, nutritional status, and, perhaps, the manufacturing source of toxaphene. Oral LD$_{50}$s in rats range from approximately 60 to 293 mg/kg (Boyd and Taylor 1971; Gaines 1969; Jones et al.

1968); however, a single oral dose of 120 mg/kg caused no toxicity in male rats (Peakall 1976). Oral LD_{50}s obtained for mice (Epstein et al. 1972) are similar to those reported for rats. Pregnant rats (Chemoff et al. 1990; Chemoff and Carver 1976) and mice (Chemoff and Carver 1976) may be more sensitive to the toxic effects of the pesticide because the approximate LD_{50}s dose is 1/2 to 1/10 of the LD_{50}s reported for nonpregnant female rats and mice.

Lackey (1949) demonstrated that the vehicle used can influence the acute toxicity of toxaphene. Death was observed in dogs administered a single gavage dose of toxaphene in corn oil at 15 mg/kg, whereas death was not seen until the dose reached 200 mg/kg when toxaphene was administered in kerosene, a poorly absorbed solvent. Furthermore, this study demonstrates that dogs may be more susceptible to the acute lethal effects of toxaphene, since the estimated oral LD_{50} is lower than that seen for other species. Intermediate and chronic exposure to toxaphene administered in feed to rats and mice indicates that mice are more sensitive to the toxic effects of the pesticides (NCI 1977). The acute oral administration of 50 mg/kg toxaphene to heifers (136- 232 kg) was fatal in 2 of 8 animals; 100 or 150 mg/kg toxaphene was fatal in 7 of 8 animals for either dose (Steele et al. 1980).

The nutritional status of the animal influences its susceptibility to the lethal effects of ingested toxaphene. Boyd and Taylor (1971) found that the oral LD_{50} for rats fed a protein- deficient diet was 80 mg/kg/day, whereas the oral LD_{50} obtained for rats fed a control diet was 220 mg/kg/day. This has important implications with regard to the possible increased susceptibility of humans who ingest a protein-deficient diet and live in areas of potential exposure to toxaphene.

The LD_{50} values and oral doses associated with death in each species after acute oral exposure are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.2 Systemic Effects

No studies regarding the musculoskeletal, dermal, or ocular effects of oral exposure to toxaphene in humans or animals were found. The systemic effects of oral toxaphene exposure are described below. The highest NOAEL values and all reliable LOAEL values for each species and duration of exposure for each effect can be found in Table 2-1 and plotted in Figure 2-1.

TABLE 2-1. Levels of Significant Exposure to Toxaphene - Oral

		Exposure		LOAEL (effect)		
Key to[a] figure	Species/ (strain)	Duration/ frequency	NOAEL System	Less Serious (mg/kg/day)	Serious (mg/kg/day)	Refe (mg/k

ACUTE EXPOSURE

	Death					
1	Rat (Wistar)	Once (GO)			80 M (LD50)	**Boyd**
2	Rat (CD)	10 d 1 x/d Gd 7-16 (GO)			35 F (31% maternal mortality rate)	**Cher**
3	Rat (Sprague- (Dawley)	10 d Gd 6-15 (GO)			32 F (50% maternal without weight loss)	Cher
4	Rat (Sherman)	Once (GO)			90 M (LD50) 80 F (LD50)	Gain
5	Mouse (CD-1)	10 d 1x/d Gd 7-16 (GO)			35 F (8% maternal mortality rate)	Cher
6	Mouse (ICR/Ha Swiss)	5 d 1x/day (GO)			40 M (death;2/12)	Epst
7	Dog (NS)	Once (GO)			15 (death;25%)	**Lack**
8	Dog (NS)	Once (GO)			200 (death;20%)	**Lack**
	Systemic					
9	Rat	10 d	Bd Wt	15 F (reduced maternal weight		**Cher**

(CD)	1x/d Gd 7-16 (GO)			gain)	
10 Rat (Sprague- Dawley)	10 d Gd 6-15 (GO)	Bd Wt		32 F (50% reduction in maternal weight gain)	Cher
11 Rat (Wistar)	Once (GO)	Hepatic		110 M (increased GGTP activity)	Gar
12 Rat (NS)	8 d ad lib (F)	Hepatic		5^{b} (decreased hepatobiliary function)	Mehe
13 Rat (NS)	Once (C)	Hepatic		120 M (increased liver weight and microsomal enzyme activity)	Peak
14 Rat (Sprague- Dawley)	14 d ad lib (F)	Bd Wt	10 M		Trot
15 Gn Pig (NS)	Once (GO)	Hepatic		300 M (increased liver weight)	Chan
	Renal			300 M (decreased kidney weight)	
	Other			300 M (decreased brain weight)	
Immuno/Lymphor					
16 Rat (Sprague- Dawley)	10 d Gd 6-15 (GO)			32 F (unspecified decreased thymus weight)	Che
17 Rat (Sprague Dawley)	14 d ad lib (F)			7.5 M (decreased thymus (weight)	Tro

	Neurological					
18	Rat (Sprague- Dawley)	3 d 1x/d (GO)			50 M (tremors)	**Rao**
	Reproductive					
19	Rat (NS)	Once (C)	120 M			**Pea**
20	Rat (CD)	10 d 1x/d Gd7-16 (GO)		15 F (reduced ossification)		**Che**
	Development					
21	Rat (Sprague- Dawley)	10 d Gd6-15 (GO)		32 F (significantly increased incidence of fetal supernumery ribs)		Cher
22	Rat (CD)	10 d 1x/d Gd7-16 (GO)		12.5 F (decrease in fetal renal protein)		Kavl
23	Mouse (CD-1)	10 d 1x/d Gd7-16 (GO)	35 F			Cher
	INTERMEDIATE EXPOSURE					
	Death					
24	Rat (Osborne- Mendel)	6 wk ad lib (F)			128 (death:40% F)	N

25	Rat (Osborne-Mendel)	6 wk ad lib (F)				128 (death;100% M & F)	N
	Mouse (B6C3F1)	6 wk ad lib (F)				42 (death;100% M & F)	NC
	Systemic						
27	Rat (Sprague-Dawley)	13 wk ad lib (F)	Hemato	45.9 M 63 F			Chu
			Hepatic	0.35^c M	1.8 M (mild anisokaryosis)	45.9 M (severe basoph anisokaryosis)	
				0.5 F	2.6 F (mild vesiculation of biliary nuclei)	63 F (severe vesi	
			Renal	0.35 M		1.8 M (tubular and interstiti necrosis, anisokaryosis pyknosis, cast formatio	
				0.50 F		12.6 F (tubular and interstit necrosis, anisokaryosis pyknosis, cast formatio	
			Endocr	1.8 M (angular collapse of follicles, increased epithelial height and reduced colloid density in the thyroid)			
				63 F (cytoplasmic vacuolation, decreased colloid density, decreased follicular size, follicular collapse, increased epithelial height in the thyroid)			
			Bd Wt	45.9 M 63 F			

28	Rat (Sprague-Dawley)	26 wk ad lib (F)	Hepatic	0.36 M 0.36 F	45 M (increased liver wt) 1.9 F (increased liver wt)	Chu
			Renal	0.36 M 0.36 F	45 M (increased kidney wt)	
			Endocr	0.36 M 0.36 F		
29	Rat (Sprague-Dawley	21 d 7d/wk 1x/d (G)	Bd Wt	6		Crow
30	Rat (Wistar)	120 d 7d/wk 1x/d (GO)	Hepatic		16.5 M (increased GGTP activity)	Garc
31	Rat (Sprague-Dawley)	39-42 wk ad lib (F)	Hepatic	1.25	5 (cytoplasmic vacuolization of hypatocytes)	Kenn
32	Rat (Sprague-Dawley)	9 wk ad lib (F)	Hepatic		15 M (12% liver weight increase and hepatic degeneration)	Koll 1983
33	Rat (Osborne-(Mendel)	6 wk ad lib (F)	Bd Wt	128		NCI
34	Rat (Sherman)	2,4,6, or 9 mo ad lib (F)	Hepatic		2.5 (centrolobular cellular hypertrophy, peripheral migration of basophilic cytoplasmic granules, fatty infiltration)	Orte 1957
			Renal	10		

35	Rat (NS)	1,3,6 mo ad lib (F)	Hepatic		2.4 M (increased organ weight and enzyme activity)	Peak
36	Mouse (Swiss Webster)	8 wk ad lib (F)	Hepatic		13 F (increased organ weight, variation in cell size with some fatty infiltration)	Alle
37	Mouse (B6C3F1)	6 wk ad lib (F)	Bd Wt	41.6		NCI
38	Dog (Beagle)	13 wk 7d/wk 1x/d (C)	Hepatic Renal	0.2 0.2	2 (hepatocellular cytoplasmic vacuolation) 2 (eosinophilic inclusions)	Chu
	Immuno./Lymphor					
39	Rat (Sprague-Dawley	9 wk ad lib (F)			1.5 M (50% decreased IgG antibody response)	Koll
40	Mouse (Swiss Webster)	8 wk ad lib (F)			13 F (decreased antibody (response)	Alle
	Neurological					
41	Rat (Sprague-Dawley	21 d 7d/wk 1x/d (GO)		6		Crow
	Reproductive					
42	Rat (Sprague-Dawley)	48 wk ad lib (F)		37 M 49 F		Chu

43	Rat (Sprague-Dawley)	39-42 wk ad lib (F)		1.25			Kenn
44	Rat (NS)	1,3,6 mo ad lib (F)		2.4 M			Peak
	Developmental						
45	Rat (Holtzman)	47 d ad lib (F)			0.05 F (behavioral effects-inferior swimming ability in developing rats)		Olso
46	Mouse (Swiss Webster)	9.5 wk ad lib (F)			1.3 F (immunosuppression in offspring)		Alle
	CHRONIC EXPOSURE						
	Death						
47	Rat (Osborne-Mendel)	80 wk ad lib (F)				27.8 M (death;6%) 27 F (death;8%)	NCI
48	Mouse (B6C3F1)	80 wk ad lib (F)				25.7 (trend toward increased mortality but individual significance not reached)	NCI
	Systemic						
49	Rat (Osborne-Mendel)	80 wk ad lib (F)	Resp		27.8 M (dyspnea) 27 F (dyspnea)		NCI
			Gastro		27.8 M (abdominal distension, 27 F diarrhea M&F)		
			Renal		27.8 M (hematuria) 27 F (hematuria)		

		Bd Wt	55.6 M	27 F (unspecified decrease in body weight)		
		Hepatic	55.6 M 54 F			
50 Mouse (B6C3F1)	80 wk ad lib (F)	Resp		12.9 (dyspnea)		NCI
		Gastro		12.9 (abdominal distension, diarrhea)		
		Bd Wt		25.7 M (decreased body weight)		
Neurological						
51 Rat (Osborne-Mendel)	80 wk ad lib (F)				27.8 M (leg paralysis, ataxia, epistaxis)	NCI
Reproductive						
52 Rat (Osborne-Mendel)	80 wk ad lib (F)			27 F (vaginal bleeding)		NCI
Cancer						
53 Rat (Osborne-Mendel)	80 wk ad lib (F)				55.6 (CEL:follicular-cell carcinomas, thyroid adenomas) 54 F (thyroid adenomas)	NCI
54 Mouse (B6C3F1)	80 wk ad lib (F)				12.9 M (hepatocellular carcinoma) 25.7 F (hepatocellular carcinoma)	NCI

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[a] The number corresponds to entries in Figure 2-1.

[b] Used to drive an acute oral MRL; dose divided by an uncertainty factor of 1,000 (10 for

variability)
resulting in an MRL of 0.005 mg/kg/day.
[c]Used to derive an intermediate oral MRL; dose divided by an uncertainty factor of 100 (1
additional modifying
factor 3 because toxaphene may after offspring behaviral and functional development, resu
ad lib = ad libitum; bd wt = body weight; (C) = Capsule; CEL = Cancer effect level; d = d
gastrointestinal; Gd = gestation day;
hemato = hematological; LD50 = lethal dose, 50% kill; mg/kg/day = milligram per kilogram
no-observable-adverse-
effect level; NS = not specified; Resp = respiratory; wk = week; wt = weight; x/d = times

TABLE 2-1. Levels of Significant Exposure to Toxaphene - Oral

Figure 2-1. Levels of Significant Exposure to Toxaphene – Oral

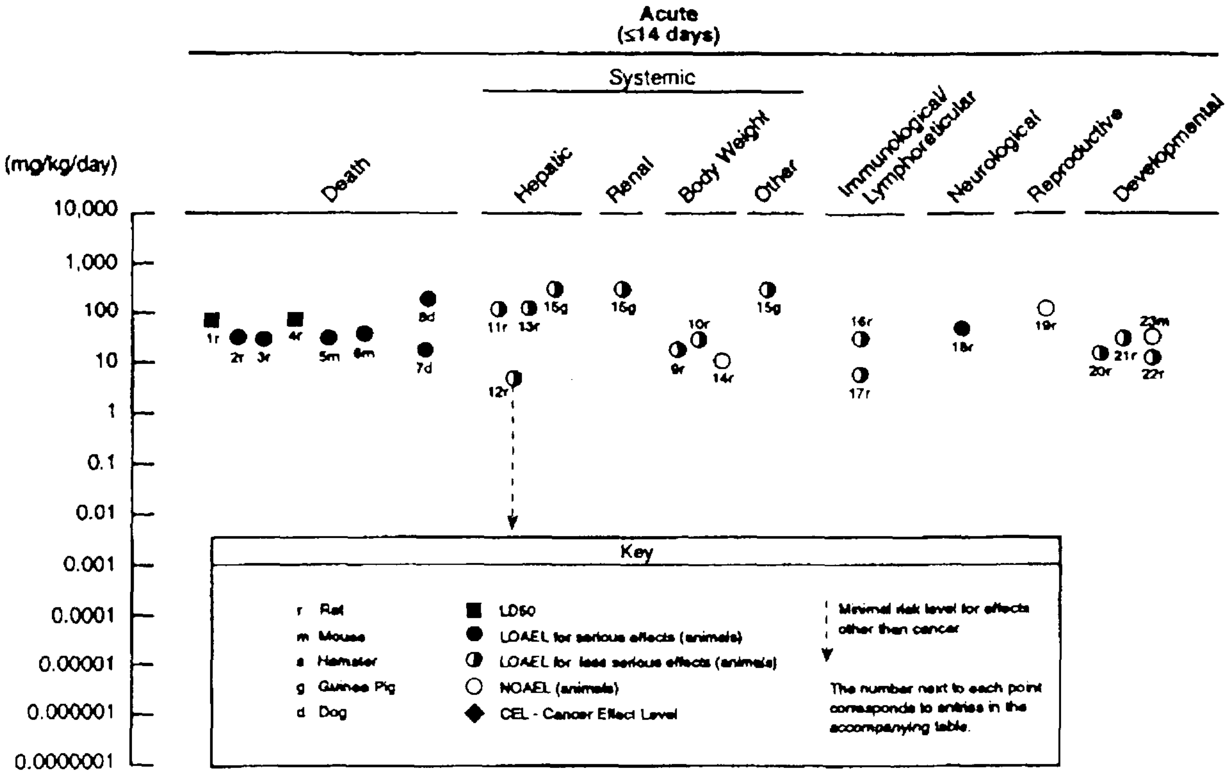


FIGURE 2-1. Levels of Significant Exposure to Toxaphene -- Oral

Figure 2-1. Levels of Significant Exposure to Toxaphene – Oral (continued)

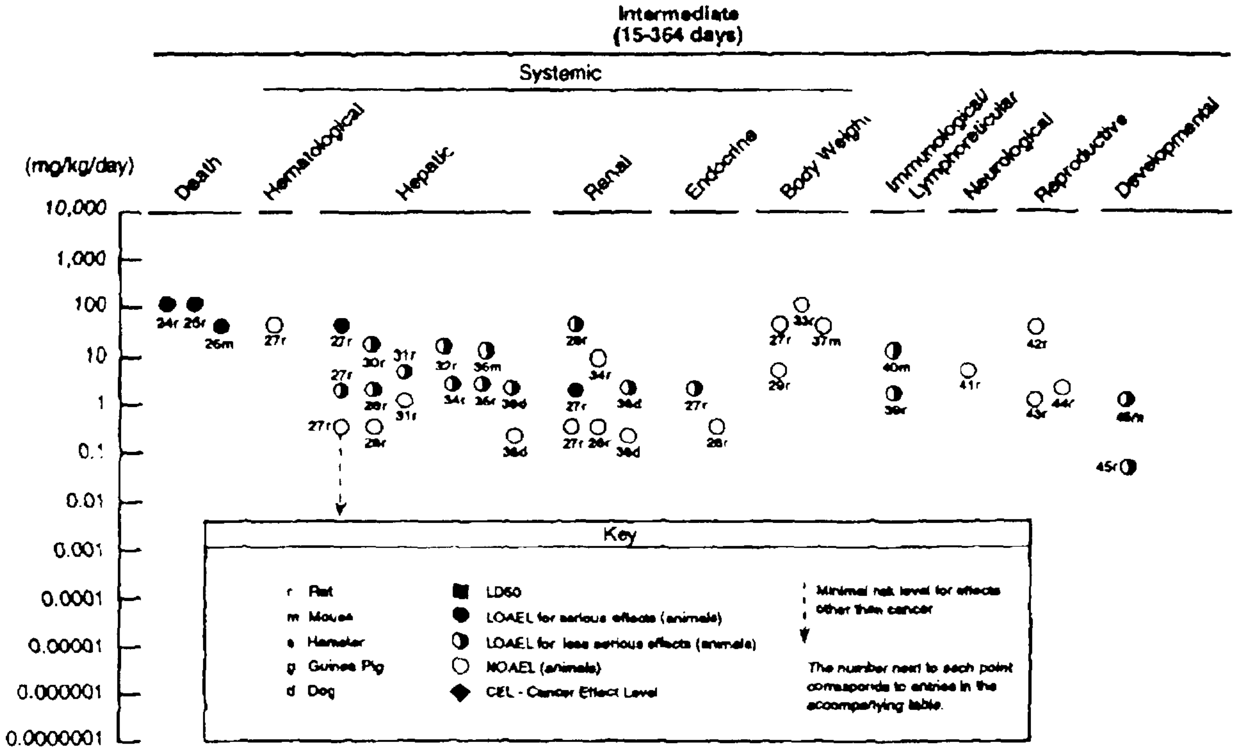
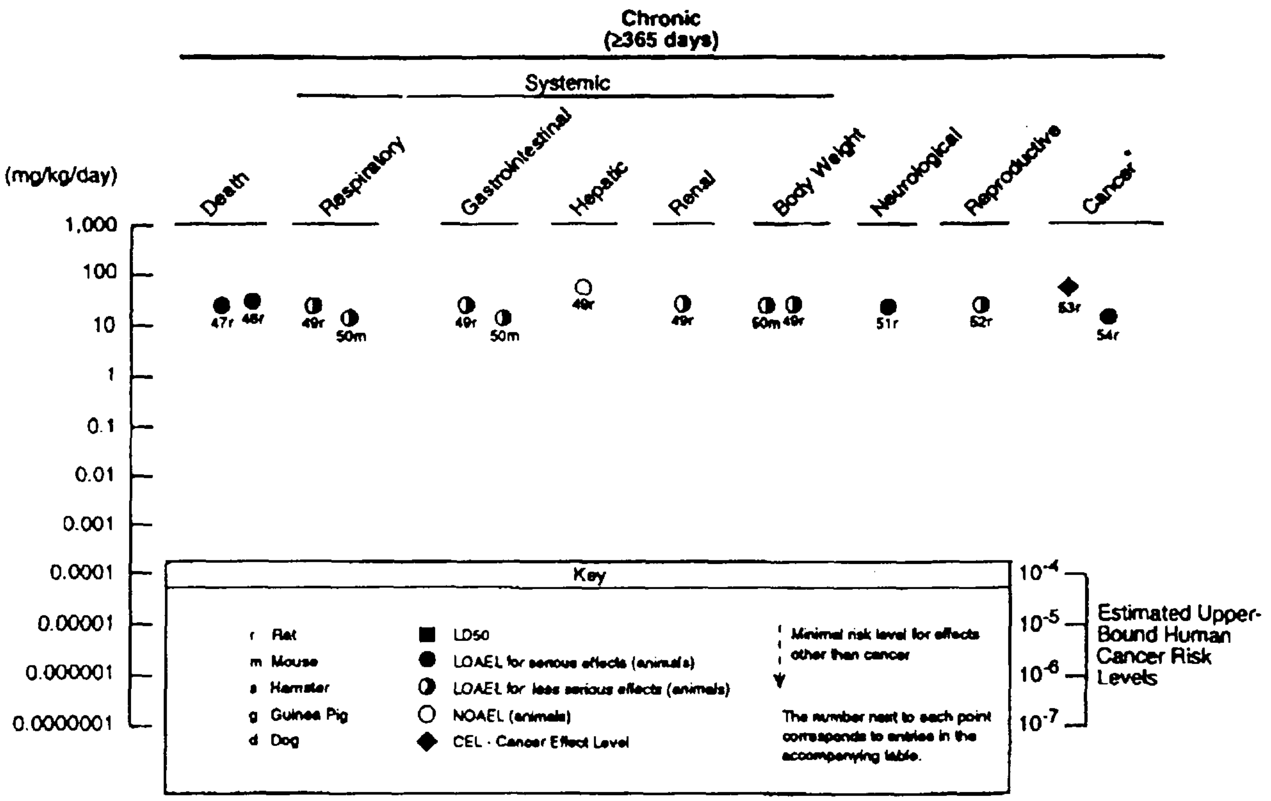


FIGURE 2-1. Levels of Significant Exposure to Toxaphene -- Oral -- continued

Figure 2-1. Levels of Significant Exposure to Toxaphene – Oral (continued)



* Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

FIGURE 2-1. Levels of Significant Exposure to Toxaphene -- Oral -- continued

Respiratory Effects. No studies were located regarding respiratory effects in humans following oral exposure to toxaphene. In rats, the acute oral administration of toxaphene has been shown to cause congestion and parenchymal hemorrhage, indicative of a generalized inflammatory response (Boyd and Taylor 1971). The study was limited by the fact that the dose was not specified. The chronic administration of toxaphene to rats or mice has been shown to cause dyspnea (NCI 1977).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following oral exposure to toxaphene. In rats, the acute oral administration of an unspecified dose of toxaphene has been shown to cause capillary congestion and capillary hemorrhage in the hearts of rats that died following treatment (Boyd and Taylor 1971). These effects are indicative of a generalized inflammatory response. In dogs, the acute oral administration of toxaphene has been reported to increase heart rate but to have no effect on the vascular system (Lackey 1949), and progressive neural degeneration has been identified in the hearts of pregnant rats following daily treatment with toxaphene during pregnancy (Badaeva 1976). However, the methods used to identify the lesions in this study are not well described and the effects were not quantitatively evaluated; therefore, these results may not be reliable.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following oral exposure to toxaphene. Gastric ulcers and local gastroenteritis (an inflammatory reaction) were observed in rats administered a single unspecified oral dose of toxaphene (Boyd and Taylor 1971). In this study, animals fed a low protein (3.5%) diet had a greater incidence of toxaphene-induced gastritis than rats fed normal chow or a test diet with a normal protein content, in keeping with the apparent "diet-dependency" of toxaphene toxicity. The chronic administration of toxaphene to rats or mice has been shown to cause gastric distension and diarrhea (NCI 1977). Thus, the results from both acute and chronic animal studies are in agreement with the known gastrointestinal effects of toxaphene in humans (gastrointestinal discomfort, nausea, vomiting, and diarrhea).

Hematological Effects. No studies were located regarding hematologic effects in humans following oral exposure to toxaphene. No adverse effects on standard hematological parameters were noted in either dogs (Chu et al. 1986; Lackey 1949) or rats (Chu et al. 1986) exposed to toxaphene for up to 2 years. Abnormalities in the blood-forming elements were observed in the spleen of rats that died following the oral administration of a single unspecified dose of toxaphene (Boyd and Taylor 1971). The authors attributed this to a generalized stress reaction. Based on the available information, it would appear that ingested toxaphene does not adversely affect the hematological status of laboratory animals.

Hepatic Effects. Little information was located regarding hepatic effects in humans following oral exposure to toxaphene. Transiently elevated liver lactate dehydrogenase and serum glumatic oxaloacetic transaminase indicative of reversible liver injury were observed in a 26-year-old man who attempted suicide by ingesting the insecticide Tox-Sol, which contains toxaphene as the active ingredient (Wells and Milhom 1983).

Adverse liver effects noted in animals following short-term oral exposure to toxaphene include increased fresh liver weight (Chandra and Durairaj 1992); inhibition of hepatobiliary function (Boyd and Taylor 1971; Mehendale 1978); and induction of hepatic microsomal enzymes with subsequent increased liver weight (Garcia and Mourelle 1984; Kinoshita et al. 1966; Peakall

1976; Trottman and Desaiah 1980; Thunberg et al. 1984). However, the majority of these studies did not report any other evidence of hepatic toxicity. Therefore, enzyme induction in the absence of other signs of liver toxicity cannot be considered adverse, but enzyme induction may precede the onset of more serious hepatic effects. Toxaphene may also induce hypoxia and alter hepatic energy metabolism because it has been shown to decrease lactate dehydrogenase activity (Gertig and Nowacyzk 1975; Kuz'minskaya and Alekhina 1976). Based on the liver toxicosis observed by Mehendale (1978), an acute oral MRL of 0.005 mg/kg/day was calulated as described in the footnote in Table 2-1. That study was chosen beacuse it reported the lowest reliable LOAEL for toxic effects of toxaphene in a target organ.

Morphological and degenerative changes have been observed in the livers of dogs, rats, and mice following intermediate-duration exposure to toxaphene (Allen et al. 1983; Chu et al. 1986, 1988; Kennedy et al. 1973; Koller et al. 1983; Lackey 1949; Ortega et al. 1957). These changes included generalized hydropic degenerative changes, cytoplasmic vacuolization, centrilobular cell hypertrophy, peripheral migration of basophilic cytoplasmic granules, and the presence of lipospheres. Hepatic enzyme induction has also been observed in rats following intermediate exposure (Garcia and Mourelle 1984; Kinoshita et al. 1966; Peakall 1976).

In keeping with toxaphene-induced induction of hepatic enzymes, the intermediate administration of toxaphene in mice is known to cause increased liver weight (Allen et al. 1983; Chu et al. 1988) and liver/body weight ratio (Chu et al. 1988). Histopathological changes were also present after intermediate toxaphene exposure, but the morphological alterations were categorized as mild and adaptive (Chu et al. 1986). In rats, intermediate exposure duration NOAELs for hepatic toxicity are generally 10-20% lower than their corresponding LOAELs (Chu et al. 1986; 1988). An intermediate exposure MRL of 0.001 mg/kg/day was derived based on the NOAEL of 0.35 mg/kg/day for hepatic toxicity in rats reported by Chu et al. (1986) and supported by Chu et al. (1988). A description of the derivation of the MRL can be found in the footnote of Table 2-1. The effects of intermediate oral administration of toxaphene to dogs include increased relative liver weight, hepatomegaly, and hepatocellular cytoplasmic vacuolation (Chu et al. 1986). That study is limited by the fact that the high-dose dogs were inadvertently fed the wrong dose for part of the study period. Biochemical and histological evidence of toxaphene-induced liver toxicosis was also observed in F_0 male and female rats in a 3-generation reproductive study (Chu et al. 1988). In that study, the F_0 generation rats were administered toxaphene for at least 26 weeks.

Liver pathology was generally observed in rats and dogs chronically administered toxaphene in the feed (Boots Hercules Agrochemicals n.d.). These changes included cytoplasmic vacuolization, slight cellular enlargement, moderate degeneration, and necrosis. In contrast, the results of a bioassay conducted in rats and mice with toxaphene failed to identify any liver pathology (NCI 1977).

Renal Effects. Little information was available regarding renal effects in humans following oral exposure to toxaphene. Renal function was temporarily compromised in a 26-year-old man who attempted suicide by ingesting an unknown quantity of toxaphene-containing pesticide (Wells and Milhorn 1983).

Toxaphene has been shown to be nephrotoxic in laboratory animals. Guinea pigs given a single oral dose of 300 mg/kg toxaphene were found to have decreased kidney weights 72 hours after treatment (Chandra and Durairaj 1992), but no ultrastructural changes were found. A single unspecified, but lethal, oral dose of toxaphene induced cloudy swelling of the proximal and distal convoluted tubules and congestion of the loop of Henle in rats (Boyd and Taylor 1971). Renal tubular injury has also been reported to occur following intermediate exposure to toxaphene. Dose- dependent injuries of the proximal convoluted tubules that were focally severe were observed in rats fed 46-63 mg/kg/day toxaphene for 13 weeks (Chu et al.1986) and increased kidney weight was observed after 26 weeks of exposure at a similar dose (Chu et al. 1988). No renal toxicosis was observed in rats at 0.36 mg/kg/day (Chu et al. 1986, 1988). Intermediate doses of toxaphene ranging from 1.8 to 9.2 mg/kg/day are also reported to cause pathological changes in the rat kidney (Chu et al. 1986). In contrast, 10 mg/kg/day was not nephrotoxic to rats (Ortega et al. 1957). Hematuria has also been observed in rats chronically administered 27 mg/kg/day toxaphene (NCI 1977), which is in keeping with the above toxaphene-related pathological changes in the kidney.

Marked degenerative fatty changes of the kidney tubular epithelium and occasional inflammation of the renal pelvis were observed in dogs following intermediate-duration exposure to 4 mg toxaphene/kg/day (Lackey 1949). Eosinophilic inclusions that were occasionally accompanied by focal necrosis have also been observed in dogs after intermediate exposure to 2 mg toxaphene/kg/day (Chu et al. 1986). These data suggest that the kidney is a target of toxaphene toxicity.

Endocrine Effects. The repeated oral administration of toxaphene to rats decreased ACTH-stimulated corticosterone synthesis in isolated or cultured adrenal cells (Mohammed et al. 1985). This effect was not seen after a single dose, suggesting that there are two mechanisms of action for toxaphene-induced depression of adrenal function, or that the effect may take time to develop. These results suggest that toxaphene, by interfering with adrenal gland function, may compromise the ability of animals or humans to respond adequately to stress. The authors suggest that *in vitro* stimulated corticosterone synthesis may be a more sensitive end point of toxaphene-induced injury than liver toxicity, but since no correlation was made between the physiological condition of those animals and the *in vitro* test results, the usefulness of the information for risk assessment is questionable. Adverse effects have been noted in the thyroid gland of rats following the subchronic oral administration of toxaphene at 1.8 mg/kg/day (Chu et al. 1986). The NOAEL for this effect under similar conditions has been reported to be 0.36 mg/kg/day (Chu et al. 1988). The morphological changes (follicular collapse, increased epithelial height with multifocal papillary proliferation, and reduced colloid density) were dose-dependent, considered mild to moderate in severity, and adaptive in nature. Their toxicological significance is not known.

Body Weight Effects. The acute administration of toxaphene to pregnant rats (Chernoff and Carver 1976; Chernoff et al. 1990) or mice decreased body weight gain (Chernoff and Carver 1976). The intermediate oral administration of 6 mg/kg/day toxaphene to male and nonpregnant female rats does not affect body weight (Crowder et al. 1980). However, higher doses orally administered to male rats have been shown to decrease body weight (Thunberg et al. 1984).

When toxaphene was administered in the feed, the NOAEL for body weight changes in rats and mice was increased compared to oral administration (NCI 1977; Chu et al. 1986; Torttman and Desaiah 1990), probably because exposure to the pesticide occurs throughout the day instead of in one bolus dose. Intermediate exposure to toxaphene caused reduced body weight in dogs (Lackey 1949), and the chronic administration of the pesticide in feed to rats and mice caused sex-specific decreases in body weight (NCI 1977).

Other Systemic Effects. Toxaphene-related decreases in brain weight have been observed following the single oral administration of 300 mg/kg toxaphene to guinea pigs (Chandra and Durairaj 1992).

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects of toxaphene in humans following oral exposure. Toxaphene has been reported to induce immunosuppressive effects (primarily humoral) in laboratory animals. Toxaphene impaired antibody (IgG) production at some, but not all, stages of the IgG response in rats (Koller et al. 1983). Similar results were obtained by Allen et al. (1983) in mice at hepatotoxic doses. However, the delayed hypersensitivity response was unaffected by toxaphene. These results suggest that toxaphene suppressed only certain components of the immune system, and therefore the immunotoxic actions of this chemical are specific rather than general. The acute administration of toxaphene to mice has also been reported to decrease thymus weight (Trottman and Desaih 1980). Additionally, thymus weight has been reported to decrease in pregnant rats following repeated oral administration of toxaphene from gestational days 6 to 15 (Chemoff et al. 1990). However the data was reported only as a change from control, and the control values were not given. Thus the relative magnitude of the changes and their biological significance could not be determined.

All reliable LOAEL values for these effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.4 Neurological Effects

Signs of central nervous system stimulation are the hallmark of acute toxaphene intoxication in both humans and animals. Case reports of accidental or intentional toxaphene ingestion indicate that toxaphene poisoning is usually accompanied by convulsive seizures that can be controlled with barbiturates or diazepam (McGee et al. 1952; Wells and Milhom 1983). The dose necessary to induce non- fatal convulsions in humans has been estimated to be approximately 10 mg/kg (Hayes 1963). Ingestion of contaminated collard greens coated with toxaphene, eaten on empty stomachs, caused convulsive seizures followed by periods of memory loss in three females aged 12-20, as well as nausea in a 49-year-old woman (McGee et al. 1952).

Convulsions have also been observed in dogs exposed to 10 mg toxaphene/kg (Lackey 1949). The acute administration of toxaphene is known to cause tremors in rats exposed to 50 mg/kg (Rao et al. 1986). Hyperreflexia has also been observed in rats (Boyd and Taylor 1971) and dogs exposed to 10 mg/kg (Lackey 1949) following acute oral exposure. Chronic administration of the pesticide has also been shown to cause tremors, leg paralysis, epistaxis, and ataxia in rats exposed to 27 (females) and 27.8 (males) mg/kg/day (NCI 1977). In heifer calves, the oral administration of toxaphene caused hyperexcitability, nystagmus, convulsions, and seizures (Steele et al. 1980).

The neurologic effects of toxaphene can also be manifested as functional (EEG, behavioral), biochemical (neurotransmitter), and morphological alterations. No effect on learning and learning transfer abilities was observed in young adult rats exposed to 6 mg toxaphene/kg (Crowder et al. 1980). The EEG pattern of squirrel monkeys is also altered by exposure to 1 mg/kg toxaphene (Santolucito 1975). In addition to affecting behavior, a dose of 120 mg toxaphene/kg has also been shown to alter brain catecholamine metabolism (Kuz'minskaya and Ivanitskii 1979). Histopathological examination of the brains of toxaphene-treated rats indicates that a dose of 12 mg/kg/day of the pesticide can also cause central nervous system cell death (Badaeva 1976). However, the methods used to identify the lesions are not well described in this study and the effects were not quantitatively evaluated; therefore, these results may not be reliable.

The highest NOAEL values and all reliable LOAEL values for neurologic effects for each species and duration category are reported in Table 2-1 and plotted in Figure 2-1.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to toxaphene.

Reproductive effects following oral exposure to toxaphene have been evaluated in multigeneration studies conducted in rats and mice. In rats, the chronic administration of toxaphene was associated with vaginal bleeding (NCI 1977). A three-generation study was conducted in which male and female rats were fed diets containing toxaphene (Kennedy et al. 1973). There were no effects on litter sizes, pup survival, weanling body weights, or reproductive indices measured. No treatment-related teratogenic effects occurred. Toxaphene caused slight cytoplasmic vacuolization in the livers of parental animals. However, no accompanying adverse effects were noted on the growth, survival, clinical parameters, and organ weights of the parents. Fertility and offspring growth and viability in rats were unaffected by toxaphene exposure (Chu et al. 1988). In male rats, the acute and intermediate exposures to toxaphene in feed did not affect circulating levels of testosterone (Peakall 1976).

A multigeneration study in which toxaphene was fed in the daily diet to Swiss mice during mating, gestation, and lactation and to pups after weaning indicated that toxaphene did not adversely affect lactation, reproduction, average litter size, and offspring growth and viability through five generations of mice (Keplinger et al. 1970). Histological examination of the livers of parental animals revealed fatty changes.

The highest NOAEL values for reproductive effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to toxaphene.

Studies were located that provided data on the developmental effects of toxaphene in laboratory animals. The results of these studies indicate that toxaphene produces matemal toxicity in rats and mice at a dose level of 15 mg/kg/day (Chemoff and Carver 1976). Although no anatomical defects in rat or mouse fetuses were reported at doses ranging from 0.05 to 75 mg/kg/day (Allen et al. 1983; Chemoff and Carver 1976; Chemoff and Kavlock 1982; Crowder et al. 1980; Kavlock et al. 1982; Olson et al. 1980), behavioral effects were reported in the offspring of rats at doses as low as 0.05 mg/kg/day (Olson et al. 1980). In mice, immunosuppression (depressed IgG antibody formation) was reported in offspring at dose levels of 13 mg/kg/day (Allen et al. 1983).

In rats, toxaphene administered by gavage at doses of 15-35 mg/kg during gestation produced 31% matemal mortality at the highest dose tested (Chemoff and Carver 1976). Toxaphene caused dose- related reductions in matemal weight gain and in the average number of stemal ossification centers in fetuses. The lack of those effects at the highest dose was probably due to the high incidence of matemal deaths effectively removing the most affected dams and fetuses. In keeping with earlier studies, 32 mg/kg toxaphene administered to pregnant rats on gestational days 6-15 caused 50% matemal mortality without affecting matemal weight gain (Chemoff et al. 1990). The offspring of the surviving animals were found to have an increase in supemumerary ribs, indicating only slight developmental toxicity. Additionally, Chemoff et al. (1990) noted a positive correlation between fetal death and decreased matemal thymus weight. However, the decreases in matemal thymus weight were transient and fetal deaths were only minimally increased in the toxaphene-treated animals. Moreover, this study was limited by the fact that 50% of the treated dams died, resulting in the teratological evaluation of the offspring from the least-affected dams. Additionally, decreases in rat fetal alkaline phosphatase activity, and reductions in total protein in fetal kidneys have been observed for prenatal toxaphene exposure (Kavlock et al. 1982). These effects suggest that toxaphene targets the developing kidney.

Exposure to toxaphene may also alter normal behavioral development. Behavioral altemations have been described for juvenile rats after perinatal exposure to low levels of toxaphene and its toxic components A and B (Olson et al. 1980). During early development, pups from all three treatment groups showed retarded maturation in the swimming test compared to controls. However, all groups displayed mature swimming behavior by postnatal day 16. Toxaphene-treated rats exhibited increased toxicity compared with those that received either toxicant A or toxicant B. That may have been due to the inability of the neonates to metabolize the complex toxaphene mixture (Olson et al. 1980).

Toxaphene administered to mice by gavage during gestation produced no adverse effects on fetal growth, viability, or gross morphology even though the toxaphene-treated dams displayed dose- dependent reductions in weight gain and increased relative liver weight (Chemoff and Carver 1976). However, toxaphene-related decreases in offspring body weight on postnatal day

1 have been observed (Chernoff and Kavlock 1982).

In a multigeneration reproduction study conducted by Keplinger et al. (1970), no adverse effects were reported on the growth and survival of the offspring in mice.

Immunosuppression in mouse offspring was reported by Allen et al. (1983) following daily dietary exposure to toxaphene before breeding, during pregnancy, and during the lactation period. At 8 weeks of age, reductions in the phagocytic ability of offspring macrophages was observed. Delayed hypersensitivity and humoral antibody responses were also suppressed in the offspring. However, no dose-response effect was observed in these assays. The relative degree of immune suppression was greatest in macrophages, followed by humoral immunity; cell-mediated immunity was least affected. Since the offspring received toxaphene transplacentally, through lactation and possibly even the feed, the actual doses of toxaphene cannot be accurately estimated. The results of the study, however, suggest that the neonates can be at risk for immunotoxicity following exposure to prolonged high dietary dosages of toxaphene, and it would be prudent to consider that potential adverse maternal and developmental effects from exposure to prolonged high dietary dosages of toxaphene could occur in humans. The highest NOAEL values and all reliable LOAEL values for development effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans following oral exposure to toxaphene.

In experimental animals, toxaphene has been found to be negative for mutagenicity using the dominant lethal test in mice (Epstein et al. 1972). No significant decrease in the number of fetal implants or increase in early fetal deaths was observed in female mice mated to male mice that had been treated with single daily oral doses of toxaphene at 40 or 80 mg/kg for 5 days prior to mating. A high mortality rate in the exposed male mice (2/12 and 9/12 for the 40 and 80 mg/kg/day groups, respectively) indicates that the doses used were sufficient to have adequately tested for mutagenicity using this assay.

Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer in humans following oral exposure to toxaphene.

Bioassays were conducted in male and female rats and mice incorporating toxaphene into the feed for 80 weeks (NCI 1977). Survival was not significantly affected by toxaphene treatment in rats. In mice, however, there was a significant trend toward decreased survival for both males and females exposed to toxaphene. Nevertheless, the number of animals at risk for the development of late- appearing tumors was sufficient. The results indicated that toxaphene caused a dose-related increase in the incidence of follicular-cell carcinomas or adenomas of the thyroid gland in male rats when compared with pooled (but not matched) controls. An increased incidence of follicular cell adenomas was also observed in female rats, but the difference was statistically significant compared with both matched and pooled controls at the high-dose only. These thyroid tumors occurred at a relatively low incidence and the control group was small. Therefore, it was concluded that the evidence that toxaphene was carcinogenic to rats is suggestive but not conclusive. However, the lesions noted in the thyroid gland in rats and dogs after subchronic treatment (Chu et al. 1986, 1988) (see Section 2.2.2.2) support the findings of the bioassay.

In the NCI (1977) bioassay, a statistically significant increase in the incidence of hepatocellular carcinomas was observed in mice using either matched or pooled controls indicating that toxaphene was carcinogenic.

One oral carcinogenicity bioassay conducted with toxaphene concluded that the pesticide was not carcinogenic; however, the study was flawed by the small number of animals used and the fact that the histological evaluations were incomplete (Triolo et al. 1982). Nevertheless, most of the available evidence suggests that toxaphene is carcinogenic in laboratory animals when administered over long periods at maximum tolerated doses.

2.2.3 Dermal Exposure

Toxaphene is apparently less toxic when applied to the skin as compared with oral administration. Dermatologists found no effects of a 10-day, 30 minutes per day exposure to an aerosol of 5% toxaphene (Keplinger 1963). Therefore, toxaphene probably has a low potential for causing skin irritation. No other reliable information regarding human dermal exposure to toxaphene was located.

2.2.3.1 Death

No studies were located regarding lethal effects in humans following dermal exposure to toxaphene. A dermal dose of 46 g has been estimated to be hazardous to humans (Hayes 1963), although it is not clear how the dose was derived. That dose is equivalent to 660 mg/kg for a 70-kg person and is approximately 10 times higher than the estimated hazardous oral dose.

The dermal LD_{50}s obtained in laboratory animals range from 780 to 4,556 mg/kg (Gaines 1969; Johnston and Eden 1953; Jones et al. 1968). Toxaphene is thus an order of magnitude less toxic by this route of exposure as compared to oral exposure. All of these studies have design and/or reporting limitations that preclude their inclusion in Table 2-2.

TABLE 2-2. Levels of Significant Exposure to Toxaphene - Dermal

	Exposure/ Duration/			LOAEL (effect)	
Species/	Frequency/	System	NOAEL	Less Serious	Serious

(Strain)	(Specific route)		(mg/kg/day)	(mg/kg/day)	(mg/kg/day)
ACUTE EXPOSURE					
Death					
Rat (Sherman)	Once				1075 M (LD50) 780 F (LD50)
Systemic					
Rabbit (New Zealand	24 hr	Dermal		3038 F (erythema, edema, and desquamation for intact group) 2025 F (erythema, edema, and desquamation for burned group)	
Rabbit (New Zealand)	4hr	Dermal		500 (erythema and edema)	
Pig (NS)	Once	Resp		13.5 (lung congestion and presence of peribronchial lymphoid follicles)	
		Renal		13.5 (cystic kidney cortex)	
Neurological					
Rabbit (New Zealand	1 d 24 hr/d		4556 F (intct) 2025 F (brnd)	6834 F (muscular weakness in intact animals)	10250 F (clon bur anim 3038 F (para in b anim
Pig (NS)	Once				13.5 (convul

d = day(s); F = female; hr = hour; LOAEL = lowest-observable-adverse-effect level; M = ma
milligram per

kilogram per day; LOAEL = lowest-observable-adverse-effect level; NOAEL = no-observable-a

TABLE 2-2. Levels of Significant Exposure to Toxaphene - Dermal

2.2.3.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, or renal effects in humans or animals following dermal exposure to toxaphene. The highest NOAEL values and all reliable LOAEL values for development effects in each species and duration category are recorded in Table 2-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans following dermal exposure to toxaphene. Toxicosis was observed in a herd of pigs that had been treated with a toxaphene solution at 10 times the recommended dose. The symptoms generally subsided when the animals were sprayed with warm water (DiPietro and Haliburton 1979). Various lung lesions were observed in three affected pigs that were not treated for toxicosis by spraying with warm water. These lesions differed in the three affected pigs examined and included congested cranial lung lobes, numerous peribronchial lymphoid follicles, and moderate congestion of the lungs. Hyperemic lungs also were observed in rabbits that died following a 24-hour dermal application of toxaphene (Industrial BioTest 1973). It should be noted that some studies performed by Industrial Biotest have been found to be less than reliable; thus the accuracy of the above data cannot be assured.

Renal Effects. No studies were located regarding renal effects in humans or animals following dermal exposure to toxaphene. In pigs, cysts were found in the renal cortex after acute dermal exposure to toxaphene 13.5 mg/kg/day (DiPietro and Haliburton 1979).

Dermal Effects. A solution of 0.5% toxaphene and 0.08% diazinon applied to the forearms or faces of volunteers was reported to be nonirritating. However, dermal application of toxaphene (90% weight to volume (w/v) ratio in xylene) to the skin of rabbits caused moderate to severe edema and erythema followed by severe desquamation following a 24-hour exposure (Industrial Biotest 1973). The skin irritation may have been caused by xylene because it has been reported to cause dermal irritation in guinea pigs (Anderson et al. 1986). Exposure to toxaphene for 4 hours caused rabbit skin to be only mildly irritated (International Research and Development Corp. 1973). This study is limited in that only unpublished summary data were available for evaluation, thereby precluding an assessment of the adequacy of the study design, conduct, and data generated.

Ocular Effects. Mild irritation to the eyelids and loss of eyelid hair was observed after 14 applications of a 20% toxaphene solution in kerosene to the eyes of rabbits and guinea pigs. The eye was not affected, and the lids cleared completely in 10 days (Boots Hercules Agrochemicals n.d.). This study is limited in that only unpublished summary data were available for evaluation, thereby precluding an assessment of the adequacy of the study design, conduct, and data generated.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunologic effects in humans or animals following dermal exposure to toxaphene.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans following dermal exposure to toxaphene.

Signs of central nervous system toxicity were observed in 40 of 150 pigs 36 hours after being sprayed with 300 mL of a 61% toxaphene solution in water (equivalent to 13.5 g/kg), which is about 10 times the recommended dose for treatment of sarcoptic mange (DiPietro and Haliburton 1979). The possibility that inhalation exposure may have also occurred cannot be ruled out. Clinical signs included head-pressing, ataxia, depression, lethargy, diarrhea, and convulsive seizures. Within a day after spraying with warm water, the animals were much improved, and complete recovery was seen within 5 days. Muscular weakness, paralysis, and convulsions were observed in rabbits exposed to a 90% w/v solution of toxaphene in xylene for 24 hours (Industrial BioTest 1973); however, this study was limited in that the solvent, xylene, was not tested alone. In the same study, the NOAEL for muscular weakness was 4556 mg/kg/day. The NOAEL dropped to 2025 mg/kg/day when the epidermis was damaged by burning.

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals following dermal exposure to toxaphene.

2.2.3.6 Developmental Effects

No studies were located regarding development effects in humans or animals following dermal exposure to toxaphene.

2.2.3.7 Genotoxic Effects

A higher incidence of chromosomal aberrations was observed in cultured lymphocytes taken from the blood of eight women exposed to toxaphene (Samosh 1974). The exposed women had entered a field that had recently been sprayed with toxaphene and were described as presenting "mild to moderate" clinical symptoms. The nature of the symptoms was not reported by Samosh. The women were likely to have been exposed by both the inhalation and dermal routes. The degree of exposure was not known.

Other genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals following dermal exposure to toxaphene.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding the absorption of toxaphene in humans or animals following inhalation exposure.

2.3.1.2 Oral Exposure

No studies were located regarding the oral absorption of toxaphene in humans. However, there is strong evidence to suggest that gastrointestinal absorption occurs in humans. Deaths and poisonings resulting from the accidental ingestion of toxaphene-contaminated food have been reported (McGee et al. 1952).

The presence of toxaphene residues in the fat of rats (Mohammed et al. 1985; Pollock and Kilgore 1980b; Saleh et al. 1979; Saleh and Casida 1978), mice (Crowder and Whitson 1980), guinea pigs, hamsters, rabbits, monkeys and chickens (Saleh et al. 1979) following ingestion indicates that absorption occurred. The identification of toxaphene in the milk of cows following ingestion is also evidence of its absorption (Clabom et al. 1963; Zweig et al. 1963).

Although there are no direct studies regarding the extent of toxaphene absorption, 56.5% of an orally administered dose was present in the feces and 9% of the dose was present in the urine of rats, mostly as metabolites. Very little was present as the parent compound, indicating that considerable metabolism had occurred and thus absorption had taken place (Chandurkhar and Matsumara 1979). Less than 10% of the administered dose was detected in tissues one day after oral administration of radiolabeled toxaphene to rats, suggesting that absorption and redistribution may have occurred over the 24 hours following administration (Crowder and Dindal 1974). That proportion of the administered dose not redistributed may have been metabolized and eliminated.

The data presented above suggest that toxaphene would be absorbed by humans following the consumption of drinking water or food contaminated with the chemical. Its absorption appears to be extensive. Its absorption is enhanced when it is dissolved in a vehicle that is readily absorbed. The bioavailability of toxaphene is increased when it is administered in or with vegetable oils like com oil or peanut oil, and the toxicity of toxaphene is potentiated (EPA 1980a). Thus, toxaphene may be more toxic when ingested in oily foods than when contaminated water is ingested.

2.3.1.3 Dermal Exposure

No studies were located in humans or animals regarding the dermal absorption of toxaphene.

However, the detection of high toxaphene levels in cow's milk (21-45 ppm) after dipping the cattle in a toxaphene solution (0.25% w/w toxaphene plus 0.03% w/v dioxathion) indicates that toxaphene was absorbed following dermal exposure (Keating 1979). Toxaphene toxicosis was reported in swine 36 hours after the dermal application of this insecticide at 10 times the recommended dose (DiPietro and Haliburton 1979).

Dermal absorption in animals was extensive following exposure to very high levels. Though the extent of absorption was not measured, the evidence suggests that absorption in humans may also be substantial following dermal exposure.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were available in humans or animals regarding the distribution of toxaphene following inhalation exposure. Although cases of inhalation exposure have been reported, there were no data that detailed distribution of toxaphene residues in various tissues.

2.3.2.2 Oral Exposure

No studies were located regarding the distribution of toxaphene following oral exposure in humans.

Results of tissue sample analysis following the oral administration of radiolabeled toxaphene to rats showed that fat is the principal storage tissue (Ohsawa et al. 1975; Pollock and Kilgore 1980b). Other evidence in animals indicates that muscle may also be a storage depot for toxaphene as suggested by the observation of a high distribution of toxaphene in muscle following an oral dose in rats, and toxaphene residues persist in muscle for up to 20 days post-administration (Crowder and Dindal 1974). The oral administration of ^{14}C-toxaphene in olive oil to rats at a dose of 10 mg/kg resulted in toxaphene residue levels of 6.4 mg/kg toxaphene and its metabolites in fat 7 days following administration. Residue levels in all other tissues were less than 0.2 mg/kg (Pollock and Kilgore 1980b). The oral administration of ^{14}C-toxaphene in corn oil to rats at doses of 19 and 8.5 mg/kg resulted in residue levels of 0.78 and 0.52 mg/kg, respectively, of toxaphene and its metabolites in fat 14 days after administration. Residue levels in all other tissues were less than 0.3 mg/kg (Ohsawa et al. 1975). Although the levels detected in fat by pollock and Kilgore (1980b) are higher than those detected by Ohsawa et al. (1975), a direct comparison cannot be made because the two studies used different sized rats, analyzed their tissues at different times after administration, and used different vehicles. Regardless of these quantitative differences, the available evidence still indicates that fat is the principal storage depot of toxaphene and its metabolites.

The highest concentration of activity, except for the gastrointestinal tract, was in the brown fat following administration of 16 mg/kg ^{14}C-toxaphene in peanut oil to rats (Mohammed et al. 1985). High concentrations of toxaphene residues were also detected in the adrenal cortex, bone marrow, liver, and kidney. Levels of radioactive residues peaked at 3 hours. At 24 hours after administration, most radioactivity was found in the white fat. Lesser amounts were detected in liver and kidney.

Mice that received an oral dose of 25 mg ^{36}Cl-toxaphene/kg in corn oil were observed to retain ^{36}Cl activity in fat, brain, kidney, liver, muscle, and testes. Levels were highest in fat (10.6 ppm) when tissues were analyzed 8 days after administration (Crowder and Whitson 1980).

Toxaphene and its metabolites have been detected in the liver, kidney, bone, brain, heart, lung, muscle, spleen, and testes of rats 14 days after the oral administration of 8.5 and 19 mg ^{14}C-toxaphene/kg (Ohsawa et al. 1975). After the oral administration of a single dose of 24 mg ^{36}C1-Toxaphene/kg to rats, the greatest levels of radioactivity were seen at 12 hours in almost all tissues. Levels in blood cells peaked after 3 days. The total fat content after 12 hours was only 0.86% of the total dose, but this exceeded the fraction of the dose found in the kidney (0.43%), testes (0.28%), and brain (0.23%) (Crowder and Dindal 1974). Approximately 77% of the dose was detected in the stomach at 12 hours, and less than 10% of the dose remained in the body after one day. At 12 hours after administration, 5.3% of the dose was present in the muscle. Although this was significantly more than the amount seen in fat and other tissues, the proportion of activity in muscle is low due to the large amount of muscle in the body. Crowder and Dindal (1974) only determined the fraction of the dose based on proportions of radioactivity found in each tissue that may have been derived from a component of the original mixture or a metabolite.

Heifer calves receiving toxaphene at oral bolus doses of 50, 100, or 150 mg ^{14}C-toxaphene/kg were found to have measurable toxaphene residues in the liver, kidney, and brain 7 days after administration. These tissues were the only ones sampled, so it is not possible to assess the amount of toxaphene that distributed to fat (Steele et al. 1980). This study showed that liver residues varied exponentially with dosage (Table 2-3). Furthermore, liver residue levels correlated with predicted fatality with an accuracy of about 80%. Based upon these tissue distribution results, the authors concluded that liver residue values could serve as a biomarker of toxaphene poisoning. Kidney and brain levels of toxaphene could not be used as biomarkers, since residue levels of the pesticide in these organs did not correlate with predicted fatality. Additionally, brain levels are not as consistent as liver values.

In investigations of effects on the adrenal gland, oral administration of 16 mg ^{14}C-toxaphene/kg of rats resulted in its distribution to the adrenal cortex. Radioactivity was primarily localized in the zona fasciculata. Only low levels of radioactivity were detected in the zona glomerulosa and the zona reticularis, and no radioactivity was found in the medulla (Mohammed et al. 1985). The zona fasciculata is responsible for glucocorticoid synthesis. A toxaphene-induced 50% inhibition of ACTH-stimulated adrenal corticosterone synthesis *in vitro* is supported by this pattern of toxaphene distribution *in vivo*. Pretreatment of rats with toxaphene in their diet for 5 weeks also resulted in a significant inhibition of corticosteroid synthesis when compared to controls. Hence, the distribution of toxaphene to the *zona fasciculata* was correlated with an adverse physiological effect.

Administration of ^{14}C-toxaphene in olive oil at a dose of 2.6 mg/kg to pregnant rats resulted in its distribution to the fat. Fetuses contained the lowest levels of radioactivity relative to other tissues analyzed (Pollock and Hillstrand 1982). After 1 day, the residue level in the fetus was 84 ppb; the residue level after 3 days averaged 28 ppb. Residue levels in the fat of the mothers exceeded 7,000 ppb. The authors reported that the overall amount of placental transfer was similar to that of PCBs, of which much less than 1% of the dose was transferred.

TABLE 2-3. Mean Toxaphene Residues (ppm) in Cows Following Oral Exposure to Toxaphene

	Toxaphene Residue		
Dose (mg/kg)	Liver (ppm)	Kidney (ppm)	Brain (ppm)
50[A]	2.88	3.45	2.67
100[B]	7.66	2.75	4.02
150[A]	22.26	5.50	3.88

[a] Values represent means of 6 animals

[b] Values represent means of 7 animals

Source: Steele et al. 1980.

TABLE 2-3. Mean Toxaphene Residues (ppm) in Cows Following Oral Exposure to Toxaphene

All studies reviewed consistently demonstrated that toxaphene was distributed throughtout the body, but it was preferentially stored in the fat. Although toxaphene has been identified in the fat up to 30 days after administration, the overall tissue activity level was very low. Apparently, toxaphene was rapidly metabolized, and its metabolites and components were not persistent. However, it is not known whether the toxaphene metabolities or the original components that persist in fat are toxic. Therefore, these persistent residues could theoretically reenter the circulation from the fat stores and cause additional delayed toxicity. In addition to its affinity for lipid tissue, it specifically localized in the *zona fasciculata* of the adrenal cortex. Although its transplacental transfer was minimal, the radioactivity that crossed the placenta also localized in the fetal adrenal. Based on the findings in all animals (Saleh et al. 1979), it would seem likely that fat would also be a principal storage depot for toxaphene in humans following its ingestion. Toxaphene localizes in the liver after initial exposure but then redistributes to fat over a longer period of time. Tissue samples obtained from a chronic dog study demonstrated that after 2 years exposure, toxaphene (as estimated from tissue chlorine levels) was measurable only in fat (Hercules Research 1966). The levels in liver, kidney, and brain were negligible. Fat samples obtained at the interim periods of 6 and 12 months had toxaphene levels comparable to those seen at 24 months, indicating that accumulation of toxaphene in adipose tissue may reach a saturation point, resulting in steady-state levels, with uptake being equivalent to excretion.

2.3.2.3 Dermal Exposure

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No studies were available in humans or animals regarding the distribution of toxaphene following dermal exposure. Although cases of dermal exposure have been reported, there were no data that listed the resulting toxaphene levels in tissues.

2.3.2.4 Other Routes of Exposure

Intravenous administration of ^{14}C-toxaphene to mice at a dose of 1.3 mg/kg resulted in the appearance of radioactivity in the liver, fat, bile, adrenal glands, kidneys, and ovaries within 20 minutes of administration. The distribution significantly changed after 4 hours with an increase in radioactivity in the abdominal fat and the intestinal contents. There were decreases in other tissues after 4 hours. Highest levels of radioactivity were still localized in the fat 16 days after administration (Mohammed et al. 1983). Autoradiographic studies of pregnant albino mice intravenously injected with ^{14}C-toxaphene (1.3 mg/kg) revealed low levels of activity in fetal tissues. This activity was highly concentrated in the fetal liver and adrenal gland. These results, as after oral administration, suggest that the transplacental transfer of toxaphene after intravenous administration is relatively low. The absorption of intravenously administered ^{14}C-toxaphene was also examined in normolipidemic and hypolipidemic female NMRI mice (Mohammed et al. 1990b). In normolipidemic mice, the radiolabel first distributed to the liver and adrenal glands 20 minutes after administration of the labeled toxaphene. After 4 hours, the label was primarily found in the abdominal fat. The distribution of the radiolabel in the hypolipidemic mice was different from the controls. After 20 minutes, the labeled toxaphene was found in the liver, adrenal gland, heart, and kidneys. After 4 hours, nearly all the label was found in the liver. The results of the study indicate that lipid metabolism may play an important role in the tissue distribution of toxaphene and thus its toxicity.

2.3.3 Metabolism

2.3.3.1 Inhalation Exposure

No studies were available in humans or animals regarding the metabolism of toxaphene following inhalation exposure.

2.3.3.2 Oral Exposure

Toxaphene is rapidly and extensively degraded in mammals following oral administration (Figure 2-2). This was clearly evident after analyzing solvent extracts from urine, feces, and tissues. In *vivo* and in *vitro* studies indicated that the principal metabolic pathways involved dechlorination, dehydrodechlorination, and oxidation. Conjugation is also likely, but it is not a major route of metabolism. Administration of ^{36}CL-toxaphene to rats at a dose of 13 mg/kg resulted in the excretion of ^{36}CL-chloride ion in the urine. This was the only metabolite identified in the urine by Ohsawa et al. (1975), and it accounted for 50% of the administered radioactivity. Results obtained with ^{36}Cl-and ^{14}C-toxaphene differed. With either label, the hexane extracts of urine and feces contained some unmetabolized material. The percentage of administered activity was negligible in urine and approximately 8-12% in feces. Hence, most excreted material consisted of metabolites from toxaphene components. The combined chloroform extracts of urine and feces contained a much higher proportion of the administered ^{14}C-activity (27%) than of the ^{36}Cl-activity (11.2%). These results indicated that the chloroform fraction consisted of partially dechlorinated metabolites, and a predominance of these products were found in the urine. The aqueous fraction contained 11.4% of the ^{14}C-dose and 0.5% of the ^{36}Cl-dose. The low amount of ^{36}Cl-activity in the aqueous extracts indicated that this fraction contained metabolites (5-10%) that had been completely dechlorinated (Ohsawa et al. 1975). About 2% of the ^{14}C-activity appeared as expired products, probably ^{14}C-carbon dioxide. Thus, these results indicate that toxaphene was metabolized mostly to partially dechlorinated products, with a small proportion being completely dechlorinated and a small proportion unmetabolized.

Pollock and Kilgore (1980b) confirmed the observations of Ohsawa et al. (1975). Less than 5% of the total activity from an orally-administered dose of 10 mg/kg dose of ^{14}C-toxaphene was extractable from urine into hexane. Thin-layer chromatography of the urine extract indicated that the components in the urine were more polar than toxaphene. No parent compounds were found in the urine. These results provide additional evidence that most of the toxaphene absorbed is metabolized, since the hexane fraction contained a low percentage of parent compound.

The complexity of toxaphene makes it difficult to understand its metabolism fully. It appears that all of its components undergo rapid metabolism, yet each component has its own rate of biotransformation. A small fraction of fecal radioactivity that was extractable into hexane indicated that some toxaphene components could be excreted unchanged. However, it is possible that some metabolite residues may share chromatographic properties similar to the original component of toxaphene.

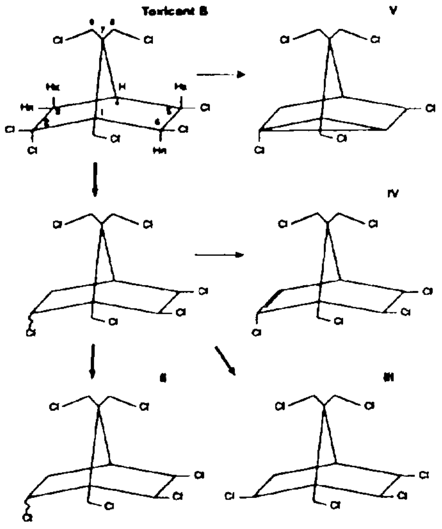
Pollock and Kilgore (1980b) also extracted the lipid tissue of rats treated with either ^{14}C-labeled toxaphene, Fraction 2, or Fraction 7. Fractions 2 and 7 are nonpolar and polar components, respectively, of toxaphene obtained from chromatographic separation of the toxaphene mixture. When compared to the chromatograms of extracts from fat fortified with ^{14}C- toxaphene, the fat of treated rats had 12% more activity in its polar region. Chromatograms of fat extracts from rats treated with each fraction indicated that two additional compounds were generated that accounted for 11% of the administered activity. With Fraction 2, the additional compounds were of greater polarity. In contrast, the additional compounds generated from Fraction 7 were less polar. The decreased polarity of these metabolites may result in their persistence in the fat and decrease the excretion of Fraction 7. It was not indicated in the study whether these new compounds were identical.

Metabolism of toxicant B (2,2,5-endo-6-exo-8,9,10-heptachlorobornane), a toxic component of toxaphene, yielded several fecal metabolites when administered orally to mice, rats, hamsters, guinea pigs, rabbits, monkeys, and chickens (Saleh et al. 1979). The greatest extent of fecal metabolites was seen in monkeys and rabbits (20%) and 3-9% in other species, indicating that species differ with respect to metabolic reate and/or pathway (Saleh et al. 1979). The large extent of metabolism seen in monkeys suggests that similar findings may result in humans; however, urinary metabolites were not monitored.

The chromatographic pattern of these fecal metabolites was characterized by short retention times, which suggested that dechlorination occurred. In several *in vitro* systems, especially in rat microsomes under anaerobic conditions with NADPH, and in rats under *in vivo* condition, toxicant B is dechlorinated at the geminal dichloro group to yield 3,5-endo-6-exo-8,9,10-hexachlorobomane (II) and 2-exo-5-endo-6-exo-8,9,10-hexachlorobomane (III) (Figure 2-2). Toxicant B is also dehydrodechlorinated to 2,5-endo-6-exo- 8,9,10-hexachlorobom-2,3,-ene (IV) and 2,5-endo- 8,9,10-pentachlorotricyclene (V) in rats *in vivo* and in other *in vitro* systems (Saleh and Casida 1978). There is no evidence that humans either do or do not metabolize toxaphene via this pathway.

Rat liver microsome did not transform metabolite I unless they were fortified with NADPH, indicating that cytochrome P-450 was required. Furthermore, the direction of metabolism was dependent upon the oxidative conditions. Only under anaerobic conditions did dechlorination of toxicant B occur to yield metabolites II and III would also be present in the feces (Saleh and Casida 1978). The hexachlorobomane ration (III/II) was relatively equivalent in the feces, fat, and liver of rats treated with toxicant B, in addition to the microsomal system. The consistency of this ratio suggested that the mechanism involved in this reaction was similar among tissues (Saleh and Casida 1978). An alternative (and perhaps more likely) explanation is that most of the metabolism occurs in the anaerobic conditions of the interstine. Then compounds II and III are absorbed and distributed to the various tissues, thus keeping the original ratio found in the intestines.

FIGURE 2-2. Proposed Metabolic Scheme for a Toxicant Isolated from Toxaphene



Toxicant B = 2,2,5 - endo - 6 - exo - 8,9,10 - heptachlorobomane
Metabolite II = 2,5 - endo - 6 - exo - 8,9,10 - hexachlorobomane
Metabolite III = 2 - exo - 5 - endo - 6 - exo - 8,9, 10 - hexachlorobomane
Metabolite IV = 2,5 - endo - 6 - exo - 8,9,10 - hexachlorobom - 2,3 - ene
Metabolite V = 2,5 - endo - 8,9,10 - pentachlorotricyclene

Source: Saleh and Casida 1978.

FIGURE 2-2. Proposed Metabolic Scheme for a Toxicant Isolated from Toxaphene

Dechlorination of toxicant B resulted under aerobic conditions in the generation of five nonhydroxyl compounds in rat microsomes fortified with NADPH (Chandurkhar and Matsumara 1979). As reported by Saleh and Casida (1978), toxicant B was metabolized to a greater extent under anaerobic conditions than under aerobic conditions. It is possible that this dechlorination reaction was representative of reductive reactions that would be more favorably executed under anaerobic conditions.

Metabolites II and III were not produced under aerobic conditions. However, other unidentified products were generated. The requirement of NADPH and anaerobic conditions for production of metabolites II and III suggested the involvement of the mixed function oxidase systems (Chandurkhar and Matsumara 1979; Saleh and Casida 1978).

Gas chromatographic results of bovine liver perfusion showed that the bovine liver can metablize toxaphene to partially dechlorinated products. These reactions occurred under aerobic conditions in a manner similar to *in vivo* conditions (Mariorino et al. 1984).

Acetonitrile extracts of feces and urine from rats receiving a single oral dose of ^{14C}-toxaphene at 15 mg/kg confirmed previously discussed findings that most of the toxaphene was metabolized. Gas-liquid chromatography-electron capture (GLC-EC) analysis of thin-layer chromatography (TLC) fractions from urine and feces revealed the presence of methylation products. This showed that fecal and urinary metabolites included acidic and other hydroxyl compounds (Chandurkhar and Matsumara 1979). Further analysis indicated that approximately 9% and 1% of the urinary and fecal metablites, respectively, were sulfate conjugates. Glucuronide conjugates comprised 9.5% and 7.5% of the urinary and fecald metabolites, respectively (Chandurkhar and Matsumara 1979), The presence of sudlfate and glucuronide conjugates supported the conclusion that oxidative metabolism metabolism occurred.

2.3.3.3 Dermal Exposure

No studies were located in humans or animals regarding the metabolism of toxaphene following dermal exposure.

2.3.4 Excreation

2.3.4.1 Inhalation exposure

No studies were available in humans or animals regarding the excretion of toxaphene following inhalation exposure.

2.3.4.2 Oral Exposure

No studies were available in humans regarding the excretion of toxaphene following oral exposure.

It is evident from distribution studies that toxaphene and its metabolites are not persistent in tissues; ^{36}Cl-labeled metabolites remained for 9 days dand ^{14}C-labeled metabolites remained 16 days in the fat of animals. Metabolism studies indicated that it is rapidly and extensively biodegraded. Consequently, the rate of toxaphene elimination is very high. Table 2- 4 summarizes excretion results from studies in which rats were orally administered radiolabeled toxaphene and its components.

The average percentage of an orally administered 20 mg/kg ^{36}Cl-toxaphene dose excreted over 9 days (approximate half-life of excretion) was 52.6%. Approximately 30% of this amount was excreted in the urine and 70% was excreted in the feces. Fecal excretion reached a plateau 2-3 days after administration. The cumulative urinary excretion steadily increased over the 9 days. Much of the activity in the urine and feces was attributable to ^{36}Cl-chloride ion. Therefore, dechlorination is a dprincipal metabolic route of toxaphene that facilitates its elimination (Crowder and Dindal 1974). In an excretion study conducted by Ohsawa et al. (1975) in rats with ^{36}Cl-toxapghene, a 14 mg/kg dose resulted in the excretion of 76% of the radioactivity after 14 days. Approximately 50% of the activity was detected in the urine. The amount of activity excreted in the urine apparently followed the pattern established by Crowder and Dindal (1974) where the cumulative urinary excretion of the dose steadily increased and eventually equalled the fecal elimination. Ohsawa et al. (1975) also found that ^{36}Cl-chloride ion appeared almost entirely in the urine. The half-time for the elimination of ^{36}Cl was 2-3 days, a rate equivalent to the excretion of ^{36}Cl-sodium chloride.

TABLE 2-4. *Summary of Excretion Data: Percent of Dose Excreted in Urine and Feces Fol Components*

Chemical	Dose (mg/kg)	Vehicle	Days After Administration	% Dose Urine	% Dose Feces	Refere
^{36}Cl-Toxaphene	20	Peanut oil/ gum acacia	1	1.5	23.4	Crowd Dinda
^{36}Cl-Toxaphene	20	Peanut oil/ gum acacia	9	15.3	37.3	Crowd Dinda
^{36}Cl-Toxaphene	14	Corn oil	14	49.1	26.9	Ohsaw
^{14}C-Toxaphene	8.5	Corn oil	14	21.3	34.7	Oshaw
^{14}C-Toxaphene	19	Corn oil	14	31.8	27.8	Oshaw
^{14}C-Toxaphene	2.6	Olive oil	5	22.0	28.3	Pollo Hills
^{14}C-Toxaphene	10	Olive oil	7	22.5	35.7	Pollo Kigor
^{14}C-Fraction 2	1	Olive oil	7	30.8	38.6	Pollo Kigor
^{14}C-Fraction 7	0.6	Olive oil	7	23.5	32.6	Pollo

						Kilgo
^{14}C-Toxicant A	0.84	Corn oil	14	28.3	38.4	Oshaw
^{14}-Toxicant B	2.6	Corn oil	9	26.7	47.8	Ohsaw

TABLE 2-4. Summary of Excretion Data: Percent of Dose Excreted in Urine and Feces Following Oral Administration to Rats of Radiolabeled Toxaphene and its Components

Rats treated orally with 8.5 mg/kg and 19 mg/kg of ^{14}C-toxaphene showed no dose-related differences with respect to the excretion of radioactivity (Ohsawa et al. 1975). After 14 days, more than 50% of the total activity was excreted. Only 8-12% of the dose detected in the feces was suspected of being parent compound. The remainder of the activity in the urine and the feces was thought to be partially or completely dechlorinated products.

Radiolabeled toxicants A and B, obtained by chromatographic separation of ^{14}C-toxaphene, were orally administered to rats at doses of 0.84 and 2.6 mg/kg, respectively. Radioactivity from the ^{14}C-radiolabeled toxicants was rapidly excreted and to a slightly greater extent than toxaphene (Ohsawa et al. 1975). Parent compounds constituted only 8.6% and 2.6% of the fecal residues of Toxicants A and B, respectively. However, the dosages used were lower than for toxaphene, and only one animal was tested.

Rats orally administered 10 mg ^{14}C-toxaphene/kg in olive oil excreted 58% of the total activity in urine and feces within 7 days after administration (Pollock and Kilgore 1980b). This agreed closely with the excretion pattern reported by Ohsawa et al. (1975). Rats were also orally administered the ^{14}C-labeled isolated fractions of toxaphene, Fraction 2 and Fraction 7. As discussed in the previous section, Fractions 2 and 7 are nonpolar and polar, respectively. Of these three compound mixtures, the greatest percentage of excreted dose was seen with Fraction 2; the least was seen with Fraction 7. The metabolites derived from polar Fraction 7 were less polar, which resulted in their greater persistence in fat and reduced their rate of excretion. In contrast, the nonpolar Fraction 2-derived polar metabolites were more rapidly excreted. Radioactivity measured in the urine of rats receiving Fraction 2 was significantly higher than from those administered Fraction 7 or toxaphene.

Another possible explanation for the unexpected order of excretion is the unexplained contribution of methanol-insoluble activity in the feces. Only the methanol-extractable activity was reported. Ohsawa et al. (1975) reported that some fecal radioactivity was methanol-insoluble and was not detected. Consequently, this may have significantly altered the measurements of total excreted activity. Less polar metabolites from Fraction 7 may be present in the methanol-insoluble extract from feces.

Excretion of radioactivity derived from ^{14}C-toxaphene in pregnant rats was found to be similar to that of virgin female rats (Pollock and Hillstrand 1982). Although there was a weight difference between the pregnant and nonpregnant rats, approximately 50% of the total activity was excreted in the urine and feces over 5 days after the oral administration of 2.6 mg/kg in olive oil. The increased amount of fatty tissue had no effect on the excretion of ^{14}C-toxaphene.

Toxaphene fed to cows in their feed at levels of 20, 60, 100, and 140 ppm for 8 weeks was excreted at all dosage levels. Residues in milk increased rapidly and reached a maximum within 4 weeks after feeding commenced. The levels of toxaphene found in milk were dose-dependent. Upon the cessation of toxaphene administration, there was a rapid decrease in toxaphene residues in the milk. The rate of decrease was the same at all dosage levels during the 1st week. Decreases in milk levels after the first week were slower for animals fed toxaphene at levels greater than 20 ppm (Claborn et al. 1963) (Table 2-5). Detectable amounts of toxaphene were found in the milk of cows 7-9 days after feeding of toxaphene at levels of 2.5-20 ppm commenced (Zweig et al. 1963). As with the higher feeding levels discussed above (Claborn et al. 1963), plateaus were achieved after the 4th week except at the lowest dose level of 2.5 ppm where a maximum was achieved at 9 days. The animals were fed toxaphene for 1-2.5 months. Toxaphene was no longer detected in the milk within 14 days after cessation of toxaphene administration (Zweig et al. 1963).

2.3.4.3 Dermal Exposure

No studies were found regarding the excretion of toxaphene in humans following dermal exposure.

Information regarding the excretion of toxaphene in animals following dermal absorption is limited. Evidence for the excretion of toxaphene in milk is evident based on a study conducted with cows that were sprayed twice daily with 1 ounce of 2.0% toxaphene oil solution or sprayed twice at 3-week intervals with 0.5% sprays of toxaphene. Residues of toxaphene in milk resulting from daily oil sprays reached a maximum after the 3rd day of spraying. When cows were sprayed twice at 3-week intervals, maximum residues in milk were detected 1 or 2 days after spraying (Claborn et al. 1963). Cows that were dipped in a solution containing 0.25% toxaphene also excreted toxaphene in the milk at levels of 27-45 ppm 1 day after dipping. Toxaphene levels fell to 5 ppm 19 days after exposure ceased (Keating 1979). The absorption, distribution, and excretion of toxaphene were evident from these studies, but insufficient information regarding the dose of toxaphene precludes any estimation of the extent and rate of excretion.

TABLE 2-5. Toxaphene Levels in Milk form Cows Fed Toxaphene in their diet^{A}

	Concentration of milk (ppm)				
	Weeks of feeding			Weeks after cessation of toxaphene feeding	
Diet concentration (ppm)	1	4	8	1	3
20	0.20	0.36	0.23	0.07	-

60	0.56	0.68	0.48	0.13	0.07
100	0.87	1.15	0.91	0.15	0.12
140	1.44	1.89	1.82	0.32	0.20

[a] Values represent means of 3 samples.
Source: Claborn et al. 1963.

TABLE 2-5. Toxaphene Levels in Milk form Cows Fed Toxaphene in their diet A

2.3.4.4 Other Routes of Exposure

Mohammed et al. (1983) reported that ^{14}C-toxaphene was rapidly distributed to most tissues and organs following intravenous administration in mice. Between 20 minutes and 4 hours after injection, there was a significant increase in the radioactivity observed in the intestinal contents. The presence of radioactivity in the intestine probably represented the biliary excretion of ^{14}C-toxaphene and its metabolites. In addition, only a fraction of the administered radioactivity was detectable in fat 16 days after administration. this was consistent with the rapid *in vitro* and *in vivo* metabolism of toxaphene (Chandurkhar and Matsumara 1979; Ohsawa et al. 1975; Pollock and Kilgore 1980b; Saleh et al. 1979; Saleh and Casida 1978). The high concentration *of radioactivity in the gall bladder from* ^{14}*C-toxaphene orally administered to quail confirmed* the likelihood that the biliary pathway plays an important role in toxaphene excretion (Biesmann et al. 1983).

Based on the rapid and extensive metabolism seen in all animals, the fate of toxaphene in humans is probably similar. The negligible quantities of parent compound in the excreta and the lack of persistence of metabolites in the tissues indicate that toxaphene and its components are readily removed from the body. Low-level exposure is not expected to cause significant harm to humans. However, theoretically, acute high level exposure may saturate metabolic pathways and consequently allow toxaphene to accumulate in the tissues for a longer period of time.

2.4 MECHANISMS OF ACTION

Toxaphene is rapidly absorbed by the gastrointestinal tract and lungs; absorption through the skin can also occur, but it is much less efficient. For that reason, the dermal doses needed to cause overt toxicity in laboratory animals are an order of magnitude higher than those causing similar toxicity following oral exposure. Toxaphene is more rapidly absorbed if it is mixed in oily (lipophilic) solvents probably because interactions with polar areas on the cell membrane are reduced. Once absorbed, toxaphene rapidly distributes to all organs of the body; however, the pesticide tends to concentrate in fatty tissues and muscle where it is slowly released over a period of weeks to months. Circulating toxaphene is primarily metabolized by hepatic mixed-function oxidases. Toxaphene and its metabolites are excreted in the feces and urine and most of it is eliminated from the body within days.

Toxaphene-induced toxicity results from a combination of factors, but the most severe effects appear to be associated with a general stimulation of the central nervous system that is manifested after acute high-dose exposure to the compound (see *Neurological Effects* in Section 2.5). The stimulation is proposed to be the result of the noncompetitive inhibition of a• aminobutyric acid-dependent chloride ion channels. δ-aminobutyric acid is believed to be an inhibitory neurotransmitter. Thus, blocking its action leads to over-activity of those neurons whose activity is modulated by • aminobutyric acid. The net result is a global increase in central nervous system activity that can result in tremors, ataxia, convulsions, and death.

2.5 RELEVANCE TO PUBLIC HEALTH

Humans living in areas surrounding hazardous waste sites may be exposed to toxaphene via ingestion of contaminated water or even ingestion of soil, particularly by children. Inhalation exposure to toxaphene via volatilization from contaminated water or soil may also occur. The possibility also exists for ingestion of contaminated foodstuffs, since toxaphene may still be used on livestock and some crops. Acute exposures to high levels may be extremely unlikely at hazardous waste sites, but would be of particular concern. The clinical signs common to both humans and animals following acute intoxication with toxaphene (e.g., salivation, hyperexcitability, behavioral changes, muscle spasms, convulsions, and death) point to the nervous system as the major target of acute toxicity. This system also appears to be affected, though to a lesser extent, following longer-term exposure in humans and animals. Other toxic manifestations of toxaphene exposure observed in humans and animals include adverse respiratory effects following inhalation exposure. Target organs of toxaphene toxicity identified in experimental animals but not humans include the liver, kidney, and, to a lesser extent, the heart and immune system.

Based on the toxicological data presented in this chapter, the minimum risk level (MRL) has been established for acute and intermediate oral exposure to toxaphene because sufficient good quality data exists for that route of exposure and those exposure periods. The MRL is considered to be a level of human exposure that is without appreciable risk to health. The MRL is often derived from animal data because adequate human data do not exist. That does not preclude the calculation of an MRL because the calculation takes into account the greater sensitivity of the human response (relative to animals) to toxic insult and the fact that there is great individual variability in the human response to toxic insult.

Using standardized methods for calculating MRLs, the acute oral exposure MRL for toxaphene is estimated to be 0.005 mg/kg/day. and the intermediate oral exposure MRL is estimated to be 0.001 mg/kg/day. The following paragraphs summarize the information that is pertinent to public health.

Minimum Risk Levels for Toxaphene.

Inhalation MRLs.

MRLs for inhalation could not be derived because of the absence of reliable data following inhalation exposure. The available data regarding inhaled toxaphene are limited because the information is derived from summaries of unpublished reports or from less than reliable investigators. Thus, an MRL for inhalation exposure could not be determined.

Oral MRLs

- An MRL of 0.005 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to toxaphene.

The MRL was based on a LOAEL of 5.0 mg/kg/day for decreased hepato-biliary function in rats treated with toxaphene in the diet for 8 days (Mehendale 1978). In this study, the livers of the treated animals were used in an isolated liver perfusion preparation. Liver function was assessed by monitoring the metabolism and biliary excretion of ^{14}C-imipramine. Both the metabolism and biliary excretion of imipramine were decreased in the toxaphene-treated rats. The choices of this end point is supported by data from other studies that have shown adverse effects on the liver following acute-duration exposure to toxaphene (Chandra and Durairaj 1992; Garcia and Mourelle 1984; Mehendale 1978; Peakall 1976). The Mehendale (1978) study was used to calculate the MRL because it reported the lowest reliable LOAEL for hepatic toxicity.

- An MRL of 0.001 mg/kg/day has been drived for intermediate-duration oral exposure (15-364 days) to toxaphene.

This MRL was based on a study by Chu et al. (1986) that examined in Sprague-Dawley rats (15 males and 30 females) the effects of 13 weeks of exposure to toxaphene in the feed. This was a multigeneration study, but only the results from the FO generation were used in the profile because the amount of toxaphene consumed by the offspring was not clearly reported. For the FO rats, toxaphene was mixed with corn oil and added to the feed at approximately 0, 4, 20, 100, or 500 ppm or 0, 0.36, 1.8 (1.9 for females), 9.2 (8.5 for females), or 45-63 (both sexes) mg/kg/day, respectively. The mg/kg/day doses were calculated by the authors after determining food consumption and body weight for those animals. The highest dose of toxaphene caused increased liver and kidney weights. Pathological changes were also observed in the liver at this dose and included severe basophilia, anisokaryosis, and vesiculation of biliary nuclei. Evidence of cell death was also observed in renal tubule cells. Increased liver weight was also observed at 1.8-1.9 mg/kg/day. No effects in the liver were observed at 0.35 mg/kg/day toxaphene. That NOAEL was supported by a similar study conducted in rats by Chu et al. (1988) that reported a NOAEL of 0.36 mg/kg/day for the same toxicity end points.

Additionally, perinatal exposure to toxaphene in Holtzman rats for 47 days (approximately gestational day 17 through postnatal day 40) impaired swimming ability on postnatal days 10, 11, and 12 (Olson et al. 1980). The results of that study indicate that toxaphene has the potential to alter offspring functional and behavioral development. For that reason, an additional modifying factor of "3" was included in the MRL derivation.

An MRL for chronic-duration oral exposure to toxaphene was not derived because a suitable NOAEL or LOAEL value could not be identified in the available literature.

Death. Toxaphene can be fatal both to humans and animals following ingestion. Death has also been observed in animals following inhalation and dermal exposure to toxaphene, but no such cases have been reported in humans. Death in humans and animals is due to respiratory arrest following convulsive seizures. The doses required to produce death are relatively large, and case reports describing the occurrence of death were found only in instances of accidental or intentional ingestion of large quantities of toxaphene-containing insecticides and in cases of ingestion of heavily contaminated foods (McGee et al. 1952). Therefore, it is likely that the risk of death is very small under conditions of long-term, low-level exposure either from ingestion of contaminated food or water or inhalation of toxaphene dusts or mists. However, Boyd and Taylor (1971) found that protein deficiency enhances the lethality of ingested toxaphene in rats, so humans consuming protein- deficient diets may represent a sensitive subpopulation (see Section 2.8).

Toxaphene is a complex mixture of at least 670 chlorinated camphenes (Jansson and Wideqvist 1983). Several of the components have been identified and, as indicated below, several are more toxic than technical grade toxaphene (Casida et al. 1974; Matsumura et al. 1975; Nelson and Matsumura 1975; Turner et al. 1975). More than a three-fold difference in toxicity was observed for LD$_{50}$s in mice after the intraperitoneal administration of various toxaphene fractions or components that differed in chemical composition, polarity, and solubility (Pollock and Kilgore 1980b). Identified toxic components of toxaphene are listed in Table 2-6. Toxaphene components A and B have been isolated and found to possess toxicity that is 6 and 14 times greater than the technical toxaphene mixture as measured by comparing intraperitoneal LD$_{50}$s in mice (Casida et al. 1974). Toxicant A has been identified as a mixture of 2,2,5-endo,6-exo,8,8,9,10- octachlorobornane and 2,2,5-endo,6-exo,8,9,9,10-octachlorobornane (Turner et al. 1975; Matsumura et al. 1975) and toxicant B has been identified as 2,2,5-endo,6-exo,8,9, 10-heptachlorobornane (Casida et al. 1974). It has further been determined that toxicant B and four of its derivatives, each with an additional chlorine atom at position 3-exo,8,9, or 10, may be responsible for the bulk of toxaphene's acute toxicity (Saleh et al. 1977). Also, animal studies suggest that detoxification of the toxaphene mixture may be more inefficient in immature animals and possibly also in children than the metabolism and detoxification of the single components such as toxicant A or B.

TABLE 2-6. Identified Toxic Components of Toxaphene

CAS Registry No./ Molecular Formula	Chemical Abstracts Name (Ninth Collective Index)	Synonyms	Reference

1∕ 7 06U2

51775-36-1/ $C_{10}H_{11}$ Cl_7	Bicyclo[2.2.1]heptane,2,2,5,6-tetrachloro-1,7,7-tris (chloromethyl)-,(5-endo, 6-exo)-	2,2,5-endo,6-exo, 8,9,10-hepta-chlorobornane; toxaphene toxicant B	Clark 1979;S and C 1978; et al. Chandu and Matsum 1979
52819-39-3/ $C_{10}H_9$ Cl_9	Bicyclo[2.2.1]heptane,2,3,3,5,6-pentachloro-7,7-bis (Chloromethy)-1-(dichloromethyl) -(2-endo,5-exo,6-exo)	Toxaphene toxicant C^*; 2-endo, 3,3,5,6-exo,8,9,10, 10-nonachlorobornane	Chandu and Ma Matsum 1979
57208-55-4/ $C_{10}H_{11}$ Cl_8	Bicyclo[2.1]heptane,2,2,5,6-tetrachloro-1,7-bis (chloromethyl)-7-(dichloromethy)-	Toxic fraction A:2,2 5-endo,6-exo,8,9,9, 10-octachlorobornane	Clark Matsum 1979
57981-30-3/ $C_{10}H_{11}$ Cl_7	Bicyclo[2.2.1]heptance2,5,6-trichloro-3,3-bis(chloromethyl) -2-(dichloromethy)-(exo,exo,exo)	2,5,6-exo,8,8,9,10 -heptachloro-dihydrocamphene	Swanso al. 19
58002-18-9/ $C_{10}H_{10}$ Cl_8	Bicyclo[2.2.1]heptane,2,2,5,6-tetrachloro-1,7-bis(chloromethyl -7-(dichloromethyl)-5-endo,6-exo,7-anti)- A-1	2,2,5-endo,6-exo,8, 8,9,10-octachlorobornane; toxaphene toxicant	Polloc Kilgor 1980b
58002-19-0/ $C_{10}H_{10}$ Cl_8	Bicyclo[2.2.1]heptane,2,2,5,6-tetrachloro-1,7-bis(chloromethyl -7-(dichloromethy)-(5-endo,6-exo,7-syn)- A-2	2,2,5-endo,6-exo,8, 8,9,10-octachlorobornane; toxaphene toxicant	Polloc Kilgor 1980b
66860-80-8/ C H	Bicyclo[2.2.1]heptane,2,3,5,6-	Toxaphene toxicant	Chandu

Cl_9	tetrachloro-7-(chlormethyl)-1-7 -bis(dichloromethyl)-(2-endo,3-exo,5-endo,6-exo,7-syn)-	Ac	al. 19
70940-135/ $C_{10}H_9$ Cl_9	Bicyclo[2.2.1]heptane,2,3,3,5,6-pentachloro-1,7-bis(chloromethyl)-7-(dischloromethyl)-	Toxaphene toxicant C_;2,3,3-endo,5,6,-exo,8,9,10,10-nonachlorobornane	Clark a Matsumu 1979

*Prepared structures have not been confirmed.
Source: EPA 1987f.

TABLE 2-6. Identified Toxic Components of Toxaphene

Systemic Effects.

Respiratory Effects. Cases of reversible allergic bronchopneumonia following insecticide exposure (including toxaphene) in aerial applicators have been reported (Warraki 1963). The available data on adverse respiratory effects associated with toxaphene exposure in animals are not conclusive (Boyd and Taylor 1971). The effects observed in humans cannot be definitively attributed to toxaphene, and they were reversible. Because there is no clear evidence that toxaphene is the causative agent and since these effects are not corroborated by animal data, their relevance to public health is not known.

Cardiovascular Effects. Adverse cardiovascular effects associated with toxaphene exposure have not been reported in humans. Animal studies have shown that acute toxaphene exposure can damage the myocardium (Boyd and Taylor 1971) as well as alter chronotropic control of the heart (Lackey 1949). Degeneration of cardiac nerve terminals has also been observed in rats exposed to toxaphene (Badaeva 1976). Nevertheless, no cardiovascular toxicity has been observed in humans exposed to toxaphene, so it is unlikely that this organ system is significantly adversely affected by the pesticide.

Hepatic Effects. Biochemical evidence of transient, reversible liver injury in a 26-year-old man who attempted suicide by drinking a toxaphene-containing insecticide was reported by Wells and Milhorn (1983). No other information regarding adverse hepatic effects in humans associated with toxaphene exposure was found. Following both short- and long-term ingestion of toxaphene by animals, hepatic hypertrophy with increased microsomal enzyme activity, inhibition of biliary excreation and function, and mild-to-moderate hepatocellular histological changes (fatty degeneration, vesiculation, vacuolation, focal necrosis) have been observed. Some authors have speculated that these changes are adaptive responses to underlying events and not direct toxic effects on the liver (Chu et al. 1986). Some of the possible mechanisms triggering these adaptive responses are as follows:

(1) As discussed in Section 2.2.2.2, toxaphene, like other chlorinated hydrocarbon insecticides,

induces hepatic microsomal enzyme activity. This could result in hepatic cell hypertrophy and liver enlargement. When separated into polar and nonpolar fractions, no difference in the extent of enzyme induction by fraction was noted (Pollock et al. 1983). Microsomal enzyme induction has important implications with regard to altering the apparent toxicity of other xenobiotics in individuals concurrently exposed to several chemicals or drugs (see Sections 2.7 and 2.8).

(2) Kuz'minskaya and Alekhina (1976) and Gertig and Nowaczyk (1975) reported that both short- and long-term oral administration of toxaphene to rats caused disturbances in energy metabolism as evidenced by changes in hepatic lactate dehydrogenase activity. However, Peakall (1979) demonstrated that these changes are not severe enough to have definite physiological consequences (measured as serum lactate and pyruvate levels) under nonstress conditions.

The results of these two studies suggest that toxaphene exposure, coupled with stress, could result in detrimental effects on hepatic energy utilization and, ultimately, in hepatic injury.

(3) Several investigators have demonstrated both *in vivo* and *in vitro* that short- and long-term toxaphene exposure is associated with inhibition of various ATPases in liver (e.g., Fattah and Crowder 1980; Mourelle et al. 1985; Trottman and Desiaiah 1979; Trottman et al. 1985). These enzymes are involved in all aspects of cellular activity, and their inhibition can ultimately result in disturbances in hepatic function, which could trigger injury responses.

Though only one case report of toxaphene-induced hepatotoxicity in humans was found in the literature, animal studies indicate that both short- and long-term exposure to toxaphene can alter hepatic function. Thus, individuals exposed to toxaphene may be at risk for compromised hepatic function and possible injury.

Renal Effects. Clinical chemistry tests indicated that renal function was temporarily compromised in a 26-year-old man who attempted suicide by ingesting a toxaphene-containing insecticide (Wells and Milhorn 1983). No other information regarding adverse renal effects in humans associated with toxaphene exposure was found. The kidney is a target organ of toxaphene toxicity following short- and long-term ingestion by animals. Toxaphene-induced adverse renal effects include cloudy swelling, congestion, tubular degeneration, focal necrosis, and kidney enlargement. Though generally more severe than the hepatic effects usually observed, these kidney lesions may also be a response to underlying changes in renal function. Several investigators have demonstrated that various ATPases in the kidney are inhibited by toxaphene (Fattah and Crowder 1980; Trottman and Desaiah 1979; Trottman et al. 1985). As discussed above, these enzymes are involved in all aspects of cellular activity, and their inhibition can ultimately result in disturbances in renal function, which could trigger injury responses.

Though only one case report of toxaphene-induced nephrotoxicity in humans was found in the literature, animal studies indicate that both short- and long-term exposure to toxaphene can alter renal function. Thus, individuals exposed to toxaphene may be at risk for compromised renal function.

Endocrine Effects. The adrenal gland appears to be adversely affected by toxaphene. One animal study has demonstrated that repeated exposure to 1.2 ppm (0.06 mg/kg/day) for 5 weeks (but not a single exposure to 16 mg/kg toxaphene) results in a decrease in ACTH-stimulated corticosterone synthesis in isolated or cultured adrenal cells (Mohammed et al. 1985). Thus, it is possible that prolonged or repeated exposure is required to affect the function of this organ. Positive results obtained following continuous (0-24-hour) exposure *in vitro* support such a conclusion. Based on these results, it is possible that adverse effects on corticosterone synthesis in humans may occur after prolonged high-level exposure to toxaphene. However, although animal data suggest that toxaphene has a potential effect on glucocorticoid activity which could alter effective energy utilization in the body, limited evidence in humans occupationally exposed to toxaphene in combination with other pesticides indicates that adrenal function is not adversely affected (Embry et al. 1972; Morgan and Roan 1973).

Results from animal studies suggest that prolonged oral exposure to toxaphene may induce thyroid injury (Chu et al. 1986, 1988; NCI 1977). The thyroid gland is essential to maintaining an organism's metabolic homeostasis, so any substance that may adversely affect the proper functioning of this organ is of concern to the health of those exposed on a prolonged basis.

Dermal Effects. Contact with toxaphene is unlikely to cause skin irritation (International Research and Development Corp. 1973).

Ocular Effects. One animal study indicated that toxaphene did not irritate the eyes (Boots Hercules Agrochemicals n.d.). Thus, it is unlikely that eye irritation or damage would result from contact with toxaphene.

Body Weight Effects. Effects of toxaphene on body weight after acute exposure are not common because changes in body weight usually take several days to appear and by then most of the acute toxic effects have disappeared. Gestational exposure to toxaphene has been reported to decrease maternal body weight gain (Chernoff and Carver 1976; Chernoff et al. 1990). Chronic exposure to low levels of toxaphene does not affect body weight, although unspecified decreases in the body weight of female rats were seen with chronic exposure. However, body weight for males was unaffected (NCI 1977). The data suggest that pregnant animals may be more sensitive to toxaphene toxicity.

Immunological and Lymphoreticular Effects. No evidence was found to indicate that toxaphene affects the immune system in humans. However, ingestion of toxaphene by laboratory animals results in specific suppression of humoral antibody (IgG) production at doses lower than those necessary to induce adverse effects in other systems (Allen et al. 1983; Koller et al. 1983). These findings could be interpreted to suggest that individuals exposed to toxaphene at levels that may not induce any other evidence of toxicity may be at risk for developing compromised immune function. However, much more data would be needed to confirm such a possibility. The oral administration of toxaphene to pregnant rats has been shown to decrease maternal thymus weight (Chernoff et al. 1990; Trottman and Desaih 1980).

Neurological Effects. Signs of central nervous system stimulation are the hallmark of acute toxaphene intoxication in both humans and animals. The dose estimated to induce non-fatal convulsions in humans is approximately 10 mg/kg (Deichmann 1973). The same dose has been observed to cause convulsions in dogs, a species considered to be sensitive to the toxic effects of toxaphene (Lackey 1949). Longer-term exposure to toxaphene can also result in less dramatic neurological effects in humans and animals. The neurologic effects of toxaphene can also be manifested as functional (EEG, behavioral), biochemical (neurotransmitter), and morphological alterations. No effect on learning and learning transfer abilities was observed in animals postnatally exposed to toxaphene. However, slight changes in motor function and behavior were observed in rats exposed perinatally (Crowder et al. 1980, see Section 2.2.2.5). Santolucito (1975) reported that the EEG pattern of squirrel monkeys was altered by chronic exposure to toxaphene.

Toxaphene-induced nervous system toxicity may result from a general disruption of nervous system function. Toxaphene has been shown to inhibit brain ATPases (Fattah and Crowder 1980; Moorthy et al. 1987; Morrow et al. 1986; Rao et al. 1986; Trottman and Desaiah 1979; Trottman et al. 1985). Morrow et al. (1986) observed that polar toxaphene fractions were more potent inhibitors of rat brain ATPase than other non-polar or intermediate polar fractions or even toxaphene itself. However, Pollock and Kilgore (1980a) reported that non-polar fractions of toxaphene are more toxic to houseflies and mice than polar fractions, which is opposite to the relationship observed by Morrow et al. (1986). Morrow et al. (1986) proposed that this discrepancy may be explained by the fact that *in vivo* the ATPases are membrane-bound in a hydrophobic environment, whereas in the *in vitro* preparation used in this study, these enzymes may have become disoriented, resulting in exposure of polar groups. Diminished ATPase activity in nervous tissue could have a profound effect on neural transmission because of the tissue's high metabolic rate.

In addition to interfering with metabolism, toxaphene has the potential to alter central nervous system neurotransmitter activity. Toxaphene acts as a noncompetitive γ-aminobutyric acid (GABA) antagonist at the chloride channel (also known as the picrotoxin binding site) in brain synaptosomes (Matsumura and Tanaka 1984; Lawrence and Casida 1984). Antagonism of GABAergic neurons within the central nervous system leads to generalized central nervous system stimulation by inhibiting chloride influx leading to hyperpolarization and increased neuronal activity. Moreover, the ability of toxaphene to induce convulsions is closely related to its affinity for the picrotoxin binding site. Toxaphene has also been shown to alter catecholamine metabolism in the brain (Kuz'minskaya and Ivanitskii 1979). Thus, toxaphene has the potential to disrupt nervous system function.

Reproductive Effects. Multigeneration studies conducted in rats (Chu et al. 1988; Kennedy et al. 1973; Peakall 1976) or mice (Keplinger et al. 1970) indicated that orally administered toxaphene does not adversely affect male or female reproductive processes.

Developmental Effects. Adverse developmental effects have been observed in laboratory animals following toxaphene ingestion at doses below those required to induce maternal toxicity. The most sensitive end points of fetal toxicity appear to be behavioral effects and immunosuppression (Allen et al. 1983; Olson et al. 1980).

Genotoxic Effects. Tables 2-7 and 2-8 present the results of *in vivo* and *in vitro* genotoxicity studies, respectively. Toxaphene has been found to be genotoxic with the Ames test for mutagenicity in the bacteria *Salmonella typhimurium* (Hooper et al. 1979; Mortelmans et al. 1986). Toxaphene increases the frequency of sister-chromatid exchanges (SCEs) of chromosomes in a cultured cell line derived from human lymphoid cells (Sobti et al. 1983). Cells in lymphocyte cultures taken from toxaphene-exposed individuals have a higher incidence of chromosomal aberrations than cultures from individuals who have not been exposed (Samosh 1974). These data suggest that toxaphene is capable of inducing genotoxic effects in humans. However, it is not known whether the genotoxic effects will be observed in human germ cells--that is, in cells capable of passing genotoxic effects on to offspring. The one study that used the dominant lethal test did not show an increase in the number of dead implants or a decrease in the number of live implants in female mice that had been mated to toxaphene-exposed males (Epstein et al. 1972). The males were exposed to toxaphene either by gavage or by intraperitoneal injection. The doses used caused death in 9 of 12 of the high-dose orally exposed mice (daily doses of 80 mg/kg for 5 days) and 2 of 9 of the high- dose intraperitoneally exposed mice (180 mg/kg single dose). Therefore, it is likely that a sufficiently high dose was tested by Epstein et al. (1972).

Toxaphene does not require metabolic activation to cause mutagenic effects in bacteria (Mortelmans et al. 1986) or to increase sister chromatid exchange in human lymphoid cell lines (Sobti et al. 1983). In fact, the addition of liver S9 fractions from Aroclor 1254-stimulated livers of rats of hamsters decreases the number of reversions in S. *typhimurium* and the incidence of SCE in the human lymphoid cell line. The findings suggest that mammalian metabolism of toxaphene may reduce the overall genotoxic effect of the mixture. The findings of Hooper et al. (1979) are of potential relevance to public health. These authors determined that certain components of the mixture of chemicals making up technical toxaphene were much less mutagenic than the mixture as a whole. Specifically, the components Hooper et al. (1979) identified as having high insecticidal or acute mammalian toxicity activity (e.g., heptachlorobornane, *gem*-dichloro components, and nonpolar fractions) were *less* mutagenic using the Ames test with *S. typhimurium* strain TA 100 than was the complete toxaphene mixture (or the polar fraction). These findings may have relevance to public health in that the components of complex mixtures such as toxaphene may distribute unevenly in the environment (see Chapter 5). The evidence discussed above suggests that toxaphene may pose a genotoxic threat to humans although it is not known whether these effects are inheritable.

TABLE 2-7. Genotoxicity of Toxaphene *In Vivo*

Species (test system)	End point	Results	Reference
Mammalian system:			
Human lymphocytes/occupational	Chromosomal	-	Samosh 1974

exposure	aberrations		
Mouse dominant lethal test	Gene mutation	-	Epstein et al. 1972

+ = positive; - = negative.

TABLE 2-7. Genotoxicity of Toxaphene In Vivo

TABLE 2-8. Genotoxicity of Toxaphene *In Vitro*

		Results		
Species (test system)	End point	With activation	Without activation	Reference
Prokaryotic organisms:				
El plasmit DNA isolated from Escherichia coli	.DNA damage	ND	-	Griffin et al. 1978
Salmonella typhimurium strain TA98	Gene mutation	ND	+	Hooper et al. 19
S. *typhimurium* strain TA100		+	-	Hooper et al. 19
S. *typhimurium* strain TA98		(+)	+	Mortelmans et al
S. *typhimurium* strain TA100		+	+	Mortelmans et al
S. *typhimurium* strain TA1535		-	-	Mortelmans et al
S. *typhimurium* strain TA1537		-	(+)	Mortelmans et al

Fungi and plant systems:				
Neurospora crassa	Gene mutation	ND	+	Mortelmans et al. 1986
Mammalian cells:				
Human lymphoid cells LAZ-007	Sister-chromatid exchange	+	+	Sobti et al. 1983

ND = no data; -= negative; += positive; (+) = weekly positive

TABLE 2-8. Genotoxicity of Toxaphene In Vitro

Cancer. No conclusive evidence is available to link cancer with toxaphene exposure in humans. However, a conclusive positive cancer bioassay was found for toxaphene administered to rodents in feed. A statistically-increased incidence of thyroid tumors was observed in rats and the incidence of hepatocellular tumors was significantly increased in mice (NCI 1977). Based on these findings, EPA (IRIS 1994) has classified toxaphene as a B2, probable human carcinogen. They derived a cancer potency factor of 1.1 mg/kg/day for both inhalation and oral exposure.

It has been proposed that organochlorines induce their carcinogenic effects via an epigenetic mechanism rather than a genotoxic mechanism (Williams 1981). One of the theories proposed to explain cancer promotion is that substances acting by this mechanism are believed to produce an effect on cell surface membranes that results in decreased intercellular communication. Without proper intercellular communication, abnormal (neoplastic) cells are allowed to proliferate unregulated.

The basis for assigning this mechanism to organochlorine pesticides includes the following observations:

- The organochlorine pesticides are generally not genotoxic.
- Often, carcinogenic effects induced by organochlorine pesticides are observed only after high and sustained levels of exposure and are sometimes reversible. This is consistent with a mechanism involving reversibly altered membranes. In contrast, genotoxic carcinogens may exert their effects even after a single exposure, at low levels of exposure, and the effects are irreversible.
- In *in vivo* carcinogenicity tests using rodents, organochlorine pesticides generally induce cancer only in the liver, whereas genotoxic carcinogens cause cancer in many organs.

While toxaphene is an organochlorine pesticide, it does not meet all the criteria of an epigenetic carcinogen. For example, toxaphene has been demonstrated to cause genotoxic effects such as microbial mutations. Furthermore, while toxaphene exposure does result in an increased incidence of hepatocellular tumors, it also has been shown to induce thyroid tumors. In conclusion, toxaphene may induce carcinogenicity via an epigenetic and a genotoxic mechanism. Furthermore, though there is no conclusive evidence to link cancer with toxaphene exposure in humans, animal evidence suggests that it may cause cancer in humans.

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to toxaphene are discussed in Section 2.6.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by toxaphene are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Toxaphene

Following acute exposure to high doses, toxaphene can be readily detected in human blood (Griffith and Blanke 1974; Taylor et al. 1979; Tewari and Sharma 1977). If exposure is via inhalation, however, absorption is probably not sufficient to yield quantifiable levels in the blood (EPA 1980a). Other body fluids in which this insecticide has been detected include breast milk, urine, and stomach washings (Munn et al. 1985; Tewari and Sharma 1977; Vaz and Blomkvist 1985). Trace amounts were found in breast milk from Swedish women (0.1 mg/kg milk fat) (Vaz and Blomkvist 1985). Only one study was found quantifying levels of toxaphene in human tissues, and none were found relating levels in the environment to levels in human fluids or tissues. Tissue samples taken from dogs sacrificed at intervals in a 2-year study demonstrated that levels of toxaphene in fat were proportional to the levels in the feed, and that tissue levels were essentially stable over the period of 2 years (Hercules Research 1966). Because toxaphene is rapidly cleared from the body, levels detected in tissues reflect only very recent exposures. Metabolites of toxaphene are excreted predominantly in the urine and feces; however, analytic procedures for detecting toxaphene metabolites are not sensitive or reliable enough to allow for screening for metabolites in the blood or excreta.

2.6.2 Biomarkers Used to Characterize Effects Caused by Toxaphene

Toxaphene causes a number of physiological effects including central nervous system excitation, liver enzyme induction, renal tubular degeneration, immune suppression, and chromosomal aberrations. However, none of these effects is specific to toxaphene exposure.

The following changes are potential biomarkers of effect for toxaphene. However, none of the observed changes is unique to toxaphene exposure. Depression of ACTH-stimulated corticosterone synthesis was observed in adrenal cells exposed to toxaphene (Mohammed et al. 1985). Also, changes in catecholamine levels are associated with adrenal toxicity (Kuz'minskaya and Ivanitskii 1979). Changes of electroencephalographic (EEG) activity may be associated with the central nervous system excitation produced by toxaphene (Santolucito 1975). Hepatic effects of toxaphene include increased microsomal enzyme activity (Chu et al. 1986) and decreased biliary excretion (Mehendale 1978). Depressed IgG production is associated with the immunosuppression caused by toxaphene in adults (Koller et al. 1983), and reduced phagocytic activity is associated with the immunosuppression observed in the newborn. Chromosomal aberrations in lymphocytes may be indicative of the genotoxic effects produced by toxaphene (Samosh 1974). Further study may indicate that one, or a combination, of the above effects may be a more specific biomarker of the effects of toxaphene.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.7 INTERACTIONS WITH OTHER SUBSTANCES

Induction of hepatic microsomal mixed-function oxidase systems is likely the basis for most of toxaphene's interactions with other chemicals, particularly other pesticides with which it is often combined. For example, Deichmann and Keplinger (1970) observed that the toxaphene 96-hour $LD_{50}S$ were increased by about ? times in rats pretreated with aldrin and dieldrin, and these values were increased by about 3 times in rats pretreated with DDT. Aldrin, dieldrin, and DDT are all known to induce microsomal enzymes. Equitoxic concentrations of toxaphene plus parathion, diazinon, or trithion yielded $LD_{50}S$ that were higher than expected based on an assumption of additivity, indicating that toxaphene antagonized the lethal effects of these three pesticides (Keplinger and Deichmann 1967).

Another example of microsomal enzyme induction by toxaphene resulting in altered activity of other chemicals was reported by Jeffery et al. (1976). They described the case of a farmer who was being treated with warfarin for thrombophlebitis and was observed to have a loss of warfarin effect that coincided with exposures to a toxaphene-lindane insecticide. The authors concluded that the toxaphene mixture induced the hepatic microsomal enzymes (for up to 3 months), thereby increasing the metabolism of warfarin.

Triolo et al. (1982) investigated the effects of toxaphene administered in the diet on benzo(a)pyrene (BP)-induced lung tumors in mice (BP was administered by oral intubation). There was no increase in the incidence of these tumors when toxaphene was administered alone, but toxaphene did significantly reduce the incidence of BP-induced lung tumors when given in combination. This reduction correlated with a toxaphene-induced reduction in BP hydroxylase activity in the lung. The results of this study suggest that toxaphene antagonizes the tumorigenic effect of BP, possibly by inhibiting the biotransformation of BP to a reactive metabolite or by promoting degradative metabolism of BP to nonactive forms in the target tissue. By this mechanism, toxaphene may have anticarcinogenic properties in mammals.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to toxaphene than will most persons exposed to the same level of toxaphene in the environment. Reasons include genetic make- up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

Data suggest that subsets of the human population may be unusually susceptible to the toxic effects of toxaphene. These include pregnant women, their fetuses, nursing babies, young children, people with neurologic diseases (particularly convulsive disorders), and individuals with protein-deficient diets. Others at increased risk include people with hepatic, cardiac, renal, or respiratory diseases, those with immune system suppression, and those ingesting alcohol or consuming therapeutic or illicit drugs.

Pregnant women, fetuses, nursing infants, and very young children may be at greater risk of adverse health effects from pesticide exposure than the general population (Calabrese 1978). Exposure to organochlorine insecticides, such as toxaphene, may adversely affect reproductive physiology (i.e., hormonal balance) in certain women (Calabrese 1978). Embryos, fetuses, and neonates up to age 2-3 months may be at increased risk of adverse effects following pesticide exposure because their enzyme detoxification systems are immature (Calabrese 1978). Animal studies suggest that detoxification of the toxaphene mixture may be less efficient in the immature human than the metabolism and detoxification of the single components such as Toxicant A or B (Olson et al. 1980). Infants and children are especially susceptible to immunosuppression because their immune systems do not reach maturity until 10-12 years of age (Calabrese 1978).

Placental transfer of toxaphene has been documented in animals (Pollock and Hillstrand 1982). Toxaphene residues have also been detected in the milk of exposed cows (Claborn et al. 1963; Zweig et al. 1963). Adverse effects have been observed in the offspring of experimental animals exposed to toxaphene during gestation and nursing. Results of experimental studies indicate that maternal toxaphene exposure may induce behavioral effects in neonates and in nursing babies (Crowder et al. 1980; Olson et al. 1980). Toxaphene exposure during gestation and nursing has been suggested to be associated with immunosuppression in offspring (Allen et al. 1983). Other effects of maternal toxaphene exposure observed in the offspring were histologic changes in fetal liver, thyroid, and kidney tissues (Chu et al. 1988).

Toxaphene exposure by inhalation, ingestion, or dermal application has induced neurotoxic effects manifested in part by seizures and other functional, biochemical, and morphological alterations (Badaeva 1976; Dille and Smith 1964; DiPietro and Haliburton 1979; Kuz'minskaya and Ivanitskii 1979; Lawrence and Casida 1984; McGee et al. 1952; Wells and Milhorn 1983). Persons with latent or clinical neurologic diseases, such as epilepsy or behavioral disorders, may be at an increased risk of adverse effects following toxaphene exposure. Children appear to be especially sensitive to the neurotoxic effects of toxaphene, as evidenced by the higher number of deaths reported following acute ingestion and subsequent convulsions (McGee et al. 1952).

Persons consuming diets deficient in protein may also be at increased risk of adverse effects from exposure to toxaphene. It has been estimated that 30% of women and 10% of men aged 30-60 ingest less than two-thirds of the RDA for protein (Calabrese 1978). An experimental study showed that central nervous system effects occurred sooner and at lower doses in rats ingesting toxaphene and diets deficient in protein (Boyd and Taylor 1971).

People with liver disease of a genetic origin (i.e., Gilbert's syndrome) and viral infections are at increased risk of developing toxic effects due to insecticide exposure (Calabrese 1978). Liver effects have been observed in both humans and animals following acute exposure to toxaphene. Liver enzymes were transiently elevated in a young man who attempted suicide by ingesting toxaphene (Wells and Milhorn 1983). Liver effects were observed in experimental studies with animals following acute, intermediate, or chronic exposure to toxaphene (Boyd and Taylor 1971; Chu et al 1986; Gertig and Nowaczyk 1975; Kennedy et al. 1973; Koller et al. 1983; Kuz'minskaya and Alekhina 1976; Lackey 1949; Mehendale 1978).

Persons with diseases that affect cardiac, renal, adrenal gland, or respiratory function may be an increased risk of adverse effects due to toxaphene exposure. Renal function was temporarily affected in a young man who attempted suicide by ingesting toxaphene (Wells and Milhorn 1983). Respiratory function was adversely affected in two men occupationally exposed to toxaphene. The heart (Kuz'minskaya and Ivanitskii 1979; Trottman et al. 1985), kidney (Boyd and Taylor 1971; Chu et al. 1986; Fattah and Crowder 1980; Trottman and Desaiah 1979; Trottman et al. 1985), and adrenal gland (Kuz'minskaya and Ivanitskii 1979; Mohammed et al. 1985) are recognized as target organs of toxaphene toxicity in experimental animals.

People susceptible to the toxic effects of toxaphene may develop compromised immune function. People with suppressed immune systems, such as found in AIDS, may also be at increased risk of developing more severe effects from toxaphene exposure. Toxaphene has produced primarily humoral immunosuppressive effects in experimental animals (Allen et al. 1983; Koller et al. 1983).

The induction of hepatic microsomal enzymes, such as mixed function oxidases, by pesticides such as toxaphene may also affect the metabolism of some drugs and alcohol (Calabrese 1978). The efficacy of prescription drugs may be reduced because of the increased rate of metabolism. For example, Jeffery et al. (1976) observed a decrease in the effectiveness of warfarin in a farmer who had been exposed to a toxaphene-lindane insecticide. Furthermore, because toxaphene is a neurotoxic agent, neurological effects associated with other agents or drugs may be exacerbated in persons exposed concomitantly to toxaphene.

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to toxaphene. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to toxaphene. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.9.1 Reducing Peak Absorption Following Exposure

Human exposure to toxaphene may occur by inhalation, ingestion, or by dermal contact. Toxaphene and other chlorinated hydrocarbons are efficiently absorbed from the gastrointestinal tract, particularly in the presence of dietary lipids. Although relatively non-volatile, absorption following inhalation exposure to dusts and sprays probably occurs through mucocilliary trapping and transport followed by gastrointestinal absorption. Dermal absorption can also be significant.

Decontamination is the first step in reducing absorption. It is recommended that decontamination begin immediately after the exposure, that contaminated clothing be removed, and that the skin, hair, and nails be washed copiously with soap and water. Leather clothing absorbs pesticides and should be discarded. Decontamination includes irrigation of the eyes with copious amounts of room- temperature water, or saline if available, for at least 15 minutes. If irritation, lacrimation, or especially pain, swelling, and photophobia persist after 15 minutes of irrigation, it is recommended that expert ophthalmologic treatment be provided.

For inhalation exposure, treatment commonly includes moving the exposed individual to fresh air, then monitoring for respiratory distress. Injuries to the lungs are more likely when there is severe respiratory irritation and persistent cough. Emergency airway support and 100% humidified supplemental oxygen with assisted ventilation may be needed.

Induced emesis may be indicated in acute ingestion unless the patient is obtunded, comatose, or convulsing. It is most effective if initiated within 30 minutes of exposure. Administration of castor oil cathartics are ill-advised because they tend to increase peristaltic activity, resulting in increased intestinal absorption of toxaphene. Adrenergic amines (decongestants, bronchodilators, or caffeine) are not recommended because they may increase myocardial irritability and produce refractory ventricular arrhythmias (Dreisbach 1983; Bryson 1986).

Gastric lavage with subsequent administration of activated charcoal and sorbitol cathartic have been recommended in acute management to reduce gastrointestinal absorption. Repeated dosing with activated charcoal or choleystyramine resin may be administered to enhance elimination by interrupting enterohepatic circulation as has been demonstrated for chlordecone and kepone (Cohn et al. 1978; Garretson et al. 1984, 1985).

Exchange transfusion, peritoneal dialysis, hemodialysis, and hemoperfusion are not likely to be beneficial because of the large volume of distribution of these chemicals, resulting in a small proportion of removable toxin.

2.9.2 Reducing Body Burden

Once absorbed, toxaphene bioaccumulates in adipose tissue and is slowly metabolized and excreted over several days to a few weeks following exposure. Prolonged treatment with cholestyramine resin beyond the initial acute exposure may be beneficial in increasing excretion by disrupting the enterohepatic recirculation and significantly reducing the total body half-life as has been demonstrated for chlordecone (Cohn W 1982).

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

The most serious toxicological effects of exposure to chlorinated hydrocarbon pesticides are central nervous system excitability. Organochlorine compounds are thought to interfere with the normal flux of sodium and potassium ions across the axon disrupting central nervous system activity resulting in generalized central nervous system excitation, which may lead to convulsions and seizures in severe cases. Toxaphene-induced central nervous system stimulation is believed to result from the noncompetitive inhibition of γ-aminobutyric acid-dependent chloride ion channels that are found on the neuron. The putative role of γ -aminobutyric acid in the central nervous system is to suppress or "put the brake on" neuronal activity. Thus, if its actions are blocked, neuronal activity increases. Unchecked neuronal excitation can lead to tremors, convulsions, seizures, and death.

Toxaphene is considered to be a moderately toxic chlorinated hydrocarbon in the same toxicity category (animal LD_{50}>50mg/kg) as DDT, chlordane, lindane, heptachlor, kepone, and mirex. Several cases of toxaphene-induced seizures in humans has been reported (McGee et al. 1952; Wells 1983). The acute management of seizures with anticonvulsants such as diazepam (a γ- aminobutyric acid agonist), phenobarbital, and phenytoin has been recommended (Schenker et al. 1992). Those drugs tend to suppress neuronal activity, thus counteracting the stimulatory effects of toxaphene. High exposures to organochlorines can lead to stimulation of the peripheral nervous system. An important result of this is cardiac arrhythmias possibly due to increased myocardial sensitivity to catacholamines (Olsen 1990). The stimulatory effects on the cardiovascular system can be reduced by the administration of propranolol, a beta-adrenergic receptor blocker (Olsen 1990).

2.10 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of toxaphene is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of toxaphene.

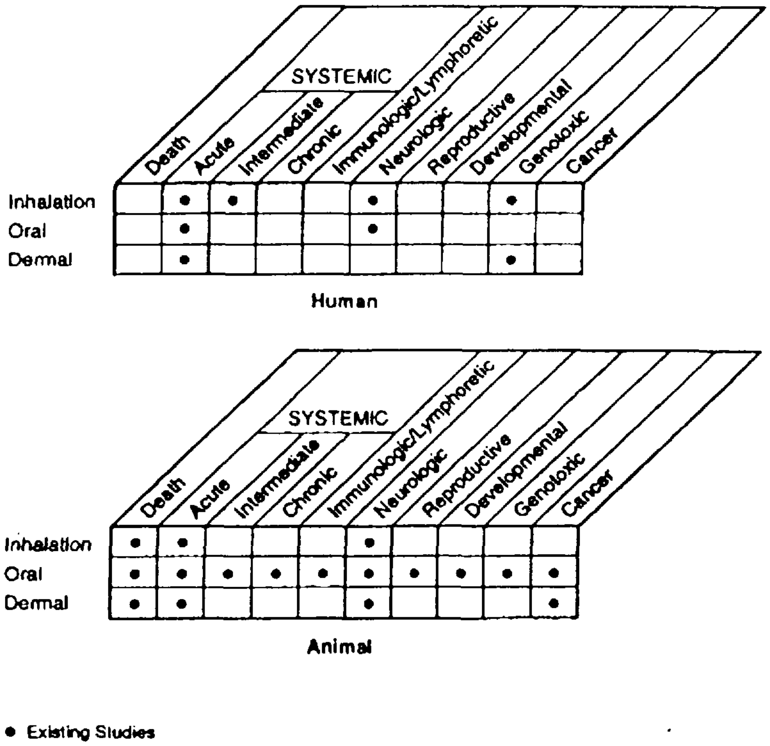
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.10.1 Existing Information on Health Effects of Toxaphene

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to toxaphene are summarized in Figure 2-3. The purpose of this figure is to illustrate the existing information concerning the health effects of toxaphene. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

The data describing the toxic effects of toxaphene in humans are generally limited to a small number of case reports of toxicity following ingestion, or dermal contact. Some controlled studies in humans exist, but the data is incomplete or unreliable. Thus, although human toxicity information exists, animal data must be considered in order to adequately assess the risk of toxaphene exposure. The database for the health effects of toxaphene following ingestion in experimental animals is substantial. However, as can be seen in Figure 2-3, very little information is available on the effects of inhalation and dermal exposure to toxaphene in animals. Furthermore, the health effects associated with acute-duration exposure are more fully characterized than those associated with intermediate or chronic-duration exposure.

FIGURE 2-3. Existing Information on Health Effects of Toxaphene



		SYSTEMIC								
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation		•	•			•			•	
Oral		•				•				
Dermal		•							•	

Human

		SYSTEMIC								
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	•	•				•				
Oral	•	•	•	•	•	•	•	•	•	•
Dermal	•	•				•				•

Animal

• Existing Studies

FIGURE 2-3. Existing Information on Health Effects of Toxaphene

2.10.2 Identification of Data Needs/

Acute-Duration Exposure. Data on the acute effects of inhaled toxaphene are probably not needed because all uses have been banned in the United States and its territories (EPA 1990). The greatest chance of exposure to toxaphene is at hazardous waste sites; therefore, it would be helpful to gather additional information in animals or humans concerning toxicity following acute dermal exposure. Data from animal studies indicate that dermal exposure to toxaphene can be lethal, but at doses that are an order of magnitude higher than those for oral administration of the pesticide (Gaines 1969; Johnston and Eden 1953; Jones et al. 1968) because absorption through the skin is much less efficient. Nevertheless, toxicity data regarding distribution and toxicity needs to be gathered so a realistic estimate of the potential health risks can be determined.

Intermediate-Duration Exposure. Limited information is available on the effects of repeated-dose exposures in both humans (inhalation and oral) and experimental animals (oral only). The exact duration and level of exposure in the human studies generally cannot be quantified because the information is derived from case reports rather than controlled studies. Most of the information on human exposure is from combinations of pesticides; only one study was located in which oral exposure to toxaphene alone was clearly linked with adverse effects in humans (McGee et al. 1952). The animal studies described predominantly neurological, hepatic, renal, developmental, and immunological end points. Sufficient data were available to calculate an oral intermediate-duration MRL. Little or no reliable information on respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, or dermal/ocular effects in animals is available. The health effects data available on inhalation and dermal exposure to toxaphene in animals come primarily from secondary unpublished sources and, therefore, do not have sufficient details for evaluation. Since both the inhalation and dermal routes are possible means of exposure for individuals living near hazardous waste sites, more information on the health effects (specifically neurological, hepatic, and renal toxicity) associated with intermediate-duration low-level inhalation and dermal exposure to toxaphene would be useful. The use of toxaphene diminished considerably after the registration for most uses was canceled in 1982, and banned in 1990 (EPA 1990b).

Chronic-Duration Exposure and Cancer. Few controlled epidemiological studies which examine the effects of chronic exposure to toxaphene have been conducted. Two well-conducted and several small-scale oral chronic toxicity/carcinogenicity bioassays have been conducted in animals (NCI 1977). These studies have found predominantly hepatic, renal, and neurological effects. The health effects data available on chronic inhalation exposure to toxaphene in animals come primarily from secondary unpublished sources, and therefore, do not have sufficient details for evaluation. No information is available on the health effects of chronic dermal exposure to toxaphene. Since these routes are a potential means of exposure for individuals living near hazardous waste sites, more information on the chronic health effects associated with chronic low-level inhalation and dermal exposure to toxaphene would be useful.

Although studies on the relationship between chronic exposure to toxaphene and cancer in humans are lacking, studies in rats and mice indicate that toxaphene causes cancer in rodents. Increased incidence of thyroid and hepatic carcinomas were observed in animals chronically exposed to toxaphene (EPA 1990b; NCI 1977). No information is available for either humans or animals on the potential cancer risk following inhalation or dermal exposure to toxaphene. Well-controlled epidemiological studies of persons exposed to toxaphene and bioassay data from chronic inhalation and dermal studies in animals would be helpful in estimating the cancer risk for persons exposed to toxaphene by these routes. Because the use of toxaphene diminished considerably since its registration for most uses was canceled in 1982 and all registered uses were banned in 1990 (EPA 1990b), the potential for additional long-term exposure is low. There appears to be little need for additional oral exposure studies since the existing database well describes the potential health effects from chronic oral exposure to toxaphene.

Genotoxicity. Two studies are available on the genotoxic effects of toxaphene in mammals: one in humans (Samosh 1974) and one in mice (Epstein et al. 1972). The results suggested that toxaphene is genotoxic in lymphocytes of humans, but no information was available on the possible genotoxic effects of toxaphene on the germ cells of humans. With the exception of the above two studies, all information on the genotoxic effects of toxaphene comes from *in vitro* studies (predominantly microbial assays; Hooper et al. 1979). More information on the genotoxic effects of toxaphene in somatic and germ cells in humans and animals would be useful because *in vitro* tests indicate that toxaphene is potentially genotoxic. Because the effects of toxaphene on mammalian germ cells are not known, it would be useful to determine whether the genotoxic effects induced by toxaphene are inheritable.

Reproductive Toxicity. No information on the reproductive effects of toxaphene in humans is available. The available information from multigeneration studies in rats indicates that toxaphene does not adversely affect reproductive end points (Keplinger et al. 1970; Kennedy et al. 1973). The available studies were well-conducted and there appears to be no need for additional oral exposure studies. Since it is likely that the distribution of dermally and orally absorbed toxaphene are similar, dermally absorbed toxaphene should not be expected to cause reproductive toxicity. Thus, further studies in that area are not warranted. Inhalation studies are also not necessary because toxaphene use is banned in the United States.

Developmental Toxicity. Information on the developmental effects of toxaphene in humans resulting from ingestion was not found. Data in experimental animals indicate that toxaphene can cause offspring behavioral toxicity (Olson et al. 1980) and immunosuppression (Allen et al. 1983) at doses that are not maternally toxic. However, only one dose was used in these studies that demonstrated behavioral effects, no NOAEL was identified, and the effects was no longer apparent after 16 weeks. Therefore, a comprehensive developmental neurobehavioral toxicity test battery may be useful in determining the potential for toxaphene to disrupt brain development. Moreover, the tests could be used to assess which central nervous system effects predominate and whether they are transient or long-lasting. Because dermal exposure is a potential means of exposure to toxaphene at hazardous waste sites, examination of developmental effects by this route is also desirable. Additionally, little is known about the kinetics of toxaphene exposure in pregnant animals, the transfer of toxaphene across the placenta, or its persistence in the fetus. That information could be used to determine if the fetus is at potentially greater risk from the effects of toxaphene.

Immunotoxicity. No information on the immunologic effects of toxaphene in humans is available. Toxaphene-related depressed IgG production has been observed in adult rats (Koller et al. 1983), and reduced phagocytic activity, which is associated with the immunosuppression, has been seen in neonates (Allen et al. 1983). A comprehensive immunological test battery in adult and neonatal animals exposed to toxaphene would help determine the potential for toxaphene to alter immunological function. Furthermore, since it is not known if the immunosuppression observed in response to toxaphene in animals is reversible, further research into this area could be helpful in determining if there are populations at higher risk because of pre-existing permanent immunosuppression (e.g., AIDS patients). In addition, additional studies on the effects on the immune system following dermal exposure would provide useful information for persons exposed in areas near hazardous waste sites.

Neurotoxicity. The available information describes neurological involvement in humans (McGee et al. 1952) and animals (Lackey 1949; Boyd and Taylor 1971; Rao et al. 1986) following short- and long-term high-level inhalation and oral exposure to toxaphene. Several mechanisms have been proposed to explain the neurotoxic effects of toxaphene, including an inhibitory effect on ATPases (Fattah and Crowder 1980; Rao et al. 1986). Very little information is available on the long-term neurotoxic effects of low-level exposure to toxaphene in humans and animals. A comprehensive adult and developmental neurobehavioral toxicity test battery may be useful in determining the potential for toxaphene to disrupt brain development. Moreover, the tests could be used to assess which central nervous system effects predominate and whether they are transient or long-lasting. Toxicity via oral and dermal routes of exposure should be assessed.

Epidemiological and Human Dosimetry Studies. Most of the available information on the effects of toxaphene in humans comes from cases of acute poisoning following the accidental or intentional ingestion of toxaphene and from occupational exposures in agricultural industries. Limitations inherent in these studies include unquantified exposure concentrations and durations, and concomitant exposure to other pesticides. Despite their inadequacies, studies in humans suggest that toxaphene, in adequate dosage, can adversely affect the liver, kidneys, lungs, and central nervous system (McGee et al. 1952). Children may be more susceptible to the toxic effects of toxaphene since most of the toxaphene-related deaths have occurred in children (McGee et al. 1952). Well- controlled epidemiological studies of people living in close proximity to areas where toxaphene has been detected at hazardous waste sites and of people exposed in the workplace could add to and clarify the existing database on toxaphene-induced human health effects. A common problem in epidemiological studies is acquisition of reliable dosimetry data on the exposed populations. For this reason, efforts to more accurately define past and current levels of exposure to toxaphene would be valuable. Follow-up of workers exposed to toxaphene may also be helpful.

Biomarkers of Exposure and Effect.

Exposure. Toxaphene levels have been measured in blood, fat, urine, and feces (Ohsawa et al.

1975; Pollack and Kilgore 1980b). No studies demonstrate a reliable correlation between blood levels and levels of exposure. Fat samples have been shown to have toxaphene levels proportional to treatment levels (Pollack and Kilgore 1980b) but fat samples are difficult to obtain from humans. Levels of toxaphene in milk fat may provide a more accurate estimate of exposure than body fat or blood (Keating 1979), but these samples can only be obtained from a small portion of the population. Because toxaphene is rapidly eliminated from the body, tissue levels are a poor estimate of any but the most immediate exposure to toxaphene. An alternate biomarker of exposure to toxaphene would be especially helpful in estimating human exposure levels. Although toxaphene is rapidly eliminated form the body via the feces and urine, persistent metabolites of toxaphene could be identified and their elimination constants determined so that urine or fecal sample could be used to determine whether or not someone has been exposed to toxaphene. One study in animals has shown that ACTH- stimulated corticosterone synthesis is depressed following repeated exposure to toxaphene at a dose lower than that required to produce adverse liver effects (Mohammed et al. 1985). This test is probably of little use since psychological state greatly influences cortisol levels.

Effect. No specific biomarkers of effects have been identified for toxaphene. Toxaphene has been demonstrated to cause a number of adverse health effects including central nervous system excitation, liver and kidney damage, and developmental and immunosuppressive effects. None of these effects is specific for toxaphene and no studies exist which demonstrate good correlation of toxaphene levels with human health effects. Neurological tests such as electroencephalographic monitoring can record levels of central nervous system activity. Liver and kidney function tests exist which detect hepatic and renal impairment. Microsomal enzyme activity may indicate early effects in the liver. Effects on the immune system can be measured by measuring immunoglobulin levels. Although each of these tests can indicate the presence of disease in the systems affected by toxaphene, the effects can be caused by a number of other disease states. This fact emphasizes the need to develop an early indicator of biological effect.

Absorption, Distribution, Metabolism, and Excretion. Quantitative evidence on the absorption of toxaphene in humans and animals following all routes of exposure is very limited. Animals dipped in toxaphene excrete the substance in the milk and also sometimes experience toxicosis (Claborn et al. 1963). Humans and animals have become seriously ill following accidental or intentional ingestion of toxaphene. The evidence clearly indicates that toxaphene is absorbed. Reports that specifically evaluate its rate or extent of absorption as a result of inhalation, oral, and dermal exposure would be useful.

No studies were located regarding the distribution of toxaphene in humans or animals following inhalation or dermal exposures. No evidence is available regarding the distribution of toxaphene in humans following ingestion. However, animal studies conducted in several species indicate that distribution following oral absorption is similar across species (Ohsawa et al. 1975; Pollock and Kilgore 1980b; Mohammed et al. 1983) and it is assumed that distribution of the pesticide in humans would be similar. Once absorbed, toxaphene and its components are distributed initially throughout the blood compartment and then to fat. Studies that investigate the distribution of toxaphene following inhalation or dermal exposure would be helpful in order to evaluate whether toxaphene behaves similarly across all routes of exposure.

Information was not available regarding the metabolism of toxaphene following dermal or inhalation exposure in animals or humans. This information would be useful for estimating health effects by these routes. Moreover, no information was available regarding the metabolites formed by humans following ingestion. Evidence from animals receiving toxaphene orally indicates that dechlorination, dehydrodechlorination, and oxidation are principal metabolic pathways (Crowder and Dindal 1974; Ohsawa et al. 1975). Although several metabolites have been isolated and identified (Ohsawa et al. 1975), several others remain unknown. Their identification will help elucidate the toxaphene metabolic pathway(s).

Quantitative information regarding the metabolites produced would suggest which biodegradation pathways are favored and provide insight into the enzyme kinetics. Information regarding the overall rate of metabolism and the rates of specific reactions would be useful. In addition, such studies might also provide information to help facilitate the metabolism of the toxaphene mixture in accidentally exposed humans.

No studies in humans were found regarding the excretion of toxaphene. Animal studies regarding the excretion of toxaphene following inhalation exposure are unavailable, but information is available for toxaphene excretion following oral and dermal exposures. Mice that received toxaphene intravenously were found to have toxaphene present in the intestinal content, suggesting biliary excretion (Mohammed et al. 1983). The presence of several metabolites in the urine and feces suggests that toxaphene degradation is extensive (Ohsawa et al. 1975; Pollock and Kilgore 1980b). Though metabolism of toxaphene facilitates its excretion, and the kinetics of toxaphene metabolism are related to the kinetics of excretion, they are not the same. Since metabolites may also contribute to the toxic effects attributed to toxaphene, it would also be beneficial to conduct studies that would establish elimination rates for each toxaphene metabolite or for similar metabolic products. In addition, such studies may also provide information to facilitate the rapid removal of toxaphene and its metabolites in exposed people.

Virtually all toxicokinetic properties reported in this profile were based on results from acute-duration exposure studies. Very limited information was available regarding intermediate-duration or chronic exposure to toxaphene. Since toxaphene is known to induce hepatic enzymes, the kinetics of metabolism during chronic exposure probably differ from those seen during acute exposure. Thus, additional studies on the metabolism of toxaphene during intermediate-duration or chronic exposure would be useful to assess the potential for toxicity following longer duration exposures.

Comparative Toxicokinetics. The absorption, distribution, metabolism, and excretion of toxaphene have been studied in animals, but only information on absorption is available in humans. In several mammalian species it is evident that toxaphene is absorbed, metabolized in the liver (with some elimination probably occurring at this point via the hepatobiliary system), and then possibly some parent compound and metabolites are distributed to fat (Ohsawa et al. 1975; Pollock and Kilgore 1980b). Very little is excreted unchanged. In studies of mammals, the extent of metabolism increased with the physiological complexity of the species. Based on this trend, humans would be expected to extensively metabolize toxaphene in a manner qualitatively similar to animals. A comprehensive investigation of metabolic pathways in lower animals would aid in the understanding of possible human kinetics.

Methods for Reducing Toxic Effects. The medical procedures used to reduce the toxic effects of toxaphene are well established and are the same as those used to treat organochlorine poisoning or poisoning due to other chemicals with central nervous system stimulatory properties. However, data on how to reduce body burden would be useful.

2.10.3 Ongoing Studies

No ongoing studies were identified that explored the health effects or toxicokinetics of toxaphene or that attempted to associate toxaphene levels in human tissues with effects.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of toxaphene is located in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of toxaphene is located in Table 3-2.

TABLE 3-1. Chemical Identity of Toxaphene

TABLE 3-2. Physical and Chemical Properties of Toxaphene[a]

Property	Information	Reference
Molecular weight	414 (avg)	DOT 1978; Worthing 1979
Color/form	Yellow, waxy, Amber	Merck 1989 DOT 1989
s		
Physical state	Solid	Merck 1989
Melting point	65-90 °C	Merck 1989

Boiling point	Not applicable (dechlorinates at 155 °C)	Merck 1989
Density at 25 °C	1.65 g/cm^3	Worthing 1979
Odor	Mild turpentine-like	HSDB 1994
	odor Pleasant piney odor	HSDB 1994
	Mild odor of chlorine and camphor	HSDB 1994
Odor threshold:		
Air	0.14 ppm (detection) 2.4	Sigworth et al. 1965
	2.4 mg/m^3	HSDB 1994
Water	0.14 mg/kg (detection)	Verschueren 1983; HSDB 1994
Solubility:		
Water	0.0003 g/100 cc	Wauchope et al. 1992
Organic solvents(s)	Freely soluble in aromatic hydrocarbons	Merck 1989; HSDB 1994
	Readily soluble in organic solvents, including petroleum oils	Worthing 1979; HSDB 1994
Partition coefficients:		
Log K_{ow}	3.3 ± 0.4	HSDB 1994
Log K_{ow}	3.30	EPA 1981a
Log K_{oc}	2.474	EPA 1981a
Log K_{oc}	5.00	Wauchope et al. 1992
Vapor pressure^b	0.2 to 0.4 mmHG at 20 °C	Mackinson et al. 1981
	0.4 mmHG at 25 °C HSDB 1994	
	4x10^6 mmHG at 20 °C	Wauchope et al. 1992

	3x10^{7} mmHG at 10 5x10^{6} mmHG at 20 °C	Suntio et al. 1981 Bidleman et al. 1981 Agrochemicals Handbook 1983
Henry,s law constant	0.21 atm-m^{3}/mol	EPA 1981a
Autoignition temperature	No data	
Flashpoint	34.4 °C 135 °C (closed cup)	DOT 1978 Mackison et al. 1981 HSDB 1994
Flammability limits in air	1.1% - 6.4% in air Solid is not flammable but is usually dissolved in combustible liquid	DOT 1978 HSDB 1994
Conversion factors (25 °C)	1 ppm x 16.89 (avg) = 1mg/m^{3} 1 mg/m^{3} x 0.059 (avg) = 1 ppm	Calculated
Explosive limits	No data	

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[a] Technical toxaphene is a complex mixture of at least 670 polychlorinated bicyclic terpe 1983; Paris and Lewis 1973). Toxaphene contains 67-69% chlorine by weight (Windholz 1983).

[b] Disagreement was found among sources for the values of vapor pressure. Four values were level. From these data it cannot be ascertained which values are correct. Measurements ma part to the discrepancy.

TABLE 3-2. Physical and Chemical Properties of Toxaphene a

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Toxaphene does not occur naturally (Canada, Department of National Health and Welfare 1978; EPA 1976a; IARC 1979). It is a complex mixture of at least 670 chlorinated terpenes (Jansson and Wideqvist 1983). Technical toxaphene can be produced commercially by reacting chlorine gas with technical camphene in the presence of ultraviolet radiation and catalysts, yielding chlorinated camphene containing 67-69% chlorine by weight (EPA 1976a; Korte et al. 1979). It has been available as a solid containing 100% technical toxaphene; a 90% solution in xylene or oil; a 40% wettable powder; 5-20% and 40% dusts; 10% and 20% granules; 4%, 6%, and 9% emulsifiable concentrates; 1% baits; a 2:1 toxaphene: DDT emulsion; and as a 14% dust containing 7% DDT (IARC 1979; IUPAC 1979; Penumarthy et al. 1976).

In 1982, EPA cancelled the registrations of toxaphene for most uses as a pesticide or pesticide ingredient except for certain uses under specific terms and conditions (EPA 1982a) and all registered uses were banned in 1990 (EPA 1990b). All registered uses were banned in 1990 (EPA 1990b). Production in 1982 was estimated at 3.7 million pounds (less than 2 million kg) (EPA 1987a). In 1972, toxaphene was the most heavily manufactured insecticide in the United States, at a production rate of 23,000 tons (21 million kg) per year (Grayson 1981). In 1976, it was produced primarily by Hercules Incorporated, Wilmington, Delaware (Penumarthy et al. 1976). Production by a total of three U.S. companies (Hercules Incorporated, Tenneco, and Vicksburg Chemical Co., a division of Vertac) during the same year totaled 19 million kg, which was a 29% decline from the 27-million-kg production level of 1975 (IARC 1979). More recently, Montgomery and Welkom (1990) listed Hercules Incorporated, Brunswick, Georgia, and Sonford Chemical Company, Port Neches, Texas, as selected manufacturers of toxaphene; however, no production estimates were provided.

Especially in the United States, the definition of "technical toxaphene" was patterned after the Hercules Inc. product (Hercules Code Number 3956) marketed under the trademark name of "Toxaphene." In recent years, Hercules Inc. has essentially let the name of toxaphene lapse into the public domain so that many products with similar properties are referred to as toxaphene (Worthing and Walker 1987). Other companies used slightly different manufacturing processes, leading to a chlorinated camphene mixture with degrees of total chlorination and a distribution of specific congeners that are not the same as the Hercules Inc. product. For instance, the toxaphene-like product commonly marketed under names like "Stroban(e)" had a slightly lowered degree of chlorination and used slightly different camphene or pinene feedstocks (Walter and Ballschmiter 1991).

Toxaphene-like pesticide agents are still produced and are widely used in many countries. While it is virtually impossible to quantify production figures or usage rates, India, many Latin American countries, former Eastern Bloc countries, countries in the former Soviet Union, and many African countries still use various toxaphene products as pesticides (Bidleman et al. 1989; Stern at al. 1993). Since toxaphene is a complex mixture, continued reliance on the use of "technical toxaphene" as a reference may actually complicate the task of identifying toxaphene signatures for contaminants transported via global atmospheric pathways.

While most attention has been focused on the intentional production of polychlorinated camphenes (PCCs) as pesticide agents, there is growing evidence that PCC congeners may be an unintentional byproduct of manufacturing processes such as those for paper and pulp that use chlorination. Studies from places as diverse as New Zealand, Japan, the Great Lakes region of the United States, and Scandinavia suggest that PCCs can be found in many parts of the world where toxaphene-mixtures were never used as pesticide agents (EPA 1993a; Jamuzi et al. 1992; Paasivirta and Rantio 1991).

Since toxaphene is a Priority Pollutant under the Clean Water Act, it is required to be included in the Toxics Release Inventory (TRI). However, since all pesticide registrations for use of toxaphene in the United States were cancelled after July 1990 (EPA 1990b), production of toxaphene has declined sharply; therefore, toxaphene has no entries associated with it in the TRI database (TRI91 1993).

4.2 IMPORT/EXPORT

No current information was found regarding the import of toxaphene into or the export of toxaphene from the United States (HSDB 1994). In 1972, 8,000 tons (7.25 million kg) of toxaphene, or 24% of annual production, were exported (USITC 1991; SRI International 1993; von Rumker et al. 1974).

4.3 USE

Toxaphene was formerly used as a nonsystemic stomach and contact insecticide with some acaricidal activity. Being nonphytotoxic (except to cucurbitus), it was used to control many insects thriving on cotton, corn, fruit, vegetables, and small grains and to control the *Cassia obtusifola* soybean pest. Toxaphene was also used to control livestock ectoparasites such as lice, flies, ticks, mange, and scab mites (Knipling and Westlake 1966; Meister 1988; Worthing 1979). Its relatively low toxicity to bees and long-persisting insecticidal effect made it particularly useful in the treatment of flowering plants. Due to its weaker action than chlordane on cockroaches, however, toxaphene was not used to control cockroaches (IARC 1979). Toxaphene was recommended at one time for use as a rodenticide (Maier-Bode 1965) and was used to eradicate fish (Muirhead-Thomson 1971). The principal use was for pest control on cotton crops (IUPAC 1979; Verschueren 1983). In 1974, an estimated 20 million kg used in the United States was distributed as follows: 85% on cotton; 7% on livestock and poultry; 5% on other field crops; 3% on soybeans; and less than 1% on sorghum (IARC 1979). Based on figures estimated by von Rumker et al. (1974) for 1972, 75% of annual toxaphene production was used for agriculture; 24% was exported; and 1% was used for industrial and commercial applications.

Toxaphene solutions were often mixed with other pesticides partly because the former appear to help solubilize other insecticides with low water solubility. Toxaphene was frequently applied with methyl or ethyl parathion, DDT, and lindane (IARC 1979; WHO 1974).

Through the early 1970s, toxaphene or mixtures of toxaphene with rotenone were used widely in lakes and streams by fish and game agencies to eliminate biologic communities that were considered undesirable for sports fishery purposes (Lockhart et al. 1992; Stern et al. 1993). This practice was especially prominent in parts of Canada and the northern United States for fish restocking experiments on smaller glacial lakes. Since the toxic effects of toxaphene may persist for many years in an aquatic system, difficulties in establishing the desired sports fisheries were among the first strong indications that toxaphene was a persistent and bioaccumulative material. Such uses of toxaphene by fish and game agencies have apparently been discontinued in the United States and Canada.

Toxaphene use in this country has witnessed a drastic decline sine 1975, when it was reported to be the most heavily used pesticide (Sanders 1975). The total used was estimated at only 9,360 tons (8.5 million kg) in 1980 and 5,400 tons (4.9 million kg) in 1982 (WHO 1984). In November 1982 EPA cancelled the registrations of toxaphene for most uses as a pesticide or pesticide ingredient (EPA 1982a). In the period following November 1982, its use was restricted to controlling scabies on sheep and cattle; use against grasshopper and army worm infestations on cotton, corn, and small grains for emergency use only (to be determined on a case-by-case basis by EPA); and controlling specific insects on banana and pineapple crops in Puerto Rico and the U.S. Virgin Islands (EPA 1982a; WHO 1984). Formulations suitable for other purposes could be sold or distributed until December 31, 1983, for use only on registered sites (EPA 1982a). The distribution or sale of remaining stocks of toxaphene formulations were permitted until December 31, 1986, for use on no-till corn, soybeans, and peanuts (to control sicklepod), dry and southern peas, and to control emergency infestations. All registered uses of toxaphene mixtures in the United States and any of its territories were cancelled in July 1990 (EPA 1990b). On September 1, 1993, all tolerances, interim tolerances, and food additive regulations for toxaphene on all agricultural commodities were revoked (EPA 1993b).

4.4 DISPOSAL

A solid waste is said to exhibit a toxicity characteristic, and is classified as a Resource Conservation and Recovery (RCRA) toxic, if an aqueous extract preformed by the legally defined procedure, from a representative sample of the waste contains toxaphene in a concentration equal to or greater than 0.5mg/L (EPA 1980b). Waste water treatment sludge and untreated process waste water generated in toxaphene production are also classified as toxic wastes. Toxaphene may not be disposed of by water or ocean dumping or by burning in the open air. The recommended disposal method is incineration in a pesticide incinerator at a temperature and residence time combination that will result in complete destruction of the chemical. Any emissions generated by incineration should meet the requirements of the Clean Air Act of 1970, and any liquids, sludges, or solid residues produced should be disposed of in accordance with federal, state, and local pollution control requirements. Municipal solid waste incinerators may be used, providing that they meet the criterion of a new pesticide incinerator and are operated under supervision (EPA 1974).

Four RCRA hazardous wastes have toxaphene as a hazardous constituent. Only one, waste exhibiting a "Toxicity characteristic" for toxaphene, has a technology-based standard under the RCRA land disposal restrictions. It must be treated by biodegradation or incineration (waste waters only) to comply with the restrictions. The three remaining wastes:

- waste water treatment sludge from the production of toxaphene,
- untreated process waste water from the production of toxaphene, and
- off-specification toxaphene (does not meet the desired chemical purity)

all have concentration-based standards that must be achieved before the waste can be land-disposed in a RCPA permitted facility (EPA 1988c).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Toxaphene is a complex mixture of at least 670 polychlorinated bicyclic terpenes consisting predominantly of chlorinated camphenes (Jansson and Wideqvist 1983; Paris and Lewis 1973). The transport and transformation of each of these components is influenced by its individual physical/chemical properties, in addition to those of the mixture as a whole. Although there are some data available in the literature that indicate selective volatilization and metabolism of individual fractions of the mixture, the environmental fate of the mixture rather than of individual components has been studied by most investigators.

Knowledge of the toxicities for specific toxaphene congeners is very limited, and standard analytical preparations of such congeners are not generally available. The situation with toxaphene is analogous to the picture for PCBs in the early 1970s. Until this situation improves, it will be very difficult to draw quantifiable toxicological conclusions about the potential impacts of toxaphene contaminants found in the environment (Bidleman et al. 1993).

Toxaphene has been widely released to the environment mainly as a result of its past use as an insecticide. The mixture partitions to the atmosphere, surface and groundwater, soil and sediment particulates, and adipose tissue. As a result of its volatility and resistance to photolytic transformation, toxaphene has been transported over long distances in the atmosphere. The mixture is relatively immobile in soils and is bioconcentrated by aquatic organisms to fairly high levels (10^4). Toxaphene also appears to be biomagnified in aquatic food chains. Toxaphene is relatively rapidly biotransformed in soils and sediments under anaerobic conditions (half-life = weeks to months). However, the mixture appears to be relatively resistant to biotransformation in these media under aerobic conditions (half-life = years).

Human exposure to toxaphene currently appears to be limited to ingestion of low concentrations of the mixture in food, particularly fish, and possibly to inhalation of ambient air. The most of the mixture in food, particularly fish, and possibly to inhalation of ambient air. The most probable populations potentially exposed to relatively high concentrations of the mixture are individuals residing in the vicinity of hazardous waste disposal sites contaminated with toxaphene.

The only other sub-populations with potentially higher exposure rates may be Eskimo groups that eat aquatic mammals that may show high body burdens of polychlorinated camphene (PCC) materials (Muir et al. 1992) and populations in poor rural areas in the southern United States that consume significant amounts of game animals (especially species like raccoons) taken from hunting or poaching (Ford and Hill 1990).

Another sub-population that could experience slightly higher levels of exposure are infants and young children who receive vitamin supplements from cod liver oil. This is of some concern in Europe where fish oil products may involve catches taken in polluted areas (Walter and Ballschmiter 1991). While no recent literature was identified on fish oil products entering U.S. markets, studies conducted in the early 1980s did detect toxaphene residues in food products that would be part of typical toddler and infant diets (Gartrell et al. 1986a, 1986b). Cod liver samples taken from the east coast of Canada have also shown measurable concentrations of toxaphene (Musial and Uthe 1983).

Toxaphene has been identified in at least 58 of the 1,430 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HAZDAT 1994). However, the number of sites evaluated for toxaphene is not known. The frequency of these sites can be seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

Toxaphene has been detected in the atmosphere, soils, surface waters and sediments, rainwater, aquatic organisms, and foodstuffs. Toxaphene has been released to the environment in the past mainly as a result of its historical use as an insecticide (EPA 1979f). Toxaphene-like mixtures of PCC congeners may also be released to the environment as unintentional by-products from manufacturing processes involving chlorination such as those used for paper and pulp. There are no known natural sources of the mixture.

Since toxaphene is a Priority Pollutant under the Clean Water Act, it is required to be included in the Toxics Release Inventory (TRI) (TRI91 1993). However, since most registered uses of toxaphene as a pesticide were cancelled in 1988 and all registered uses were cancelled in the United States and its territories after 1990, production of toxaphene has declined sharply, so that toxaphene has no entries associated with it in the TRI database (TRI91 1993).

FIGURE 5-1. FREQUENCY OF NPL SITES WITH TOXAPHENE CONTAMINATION *

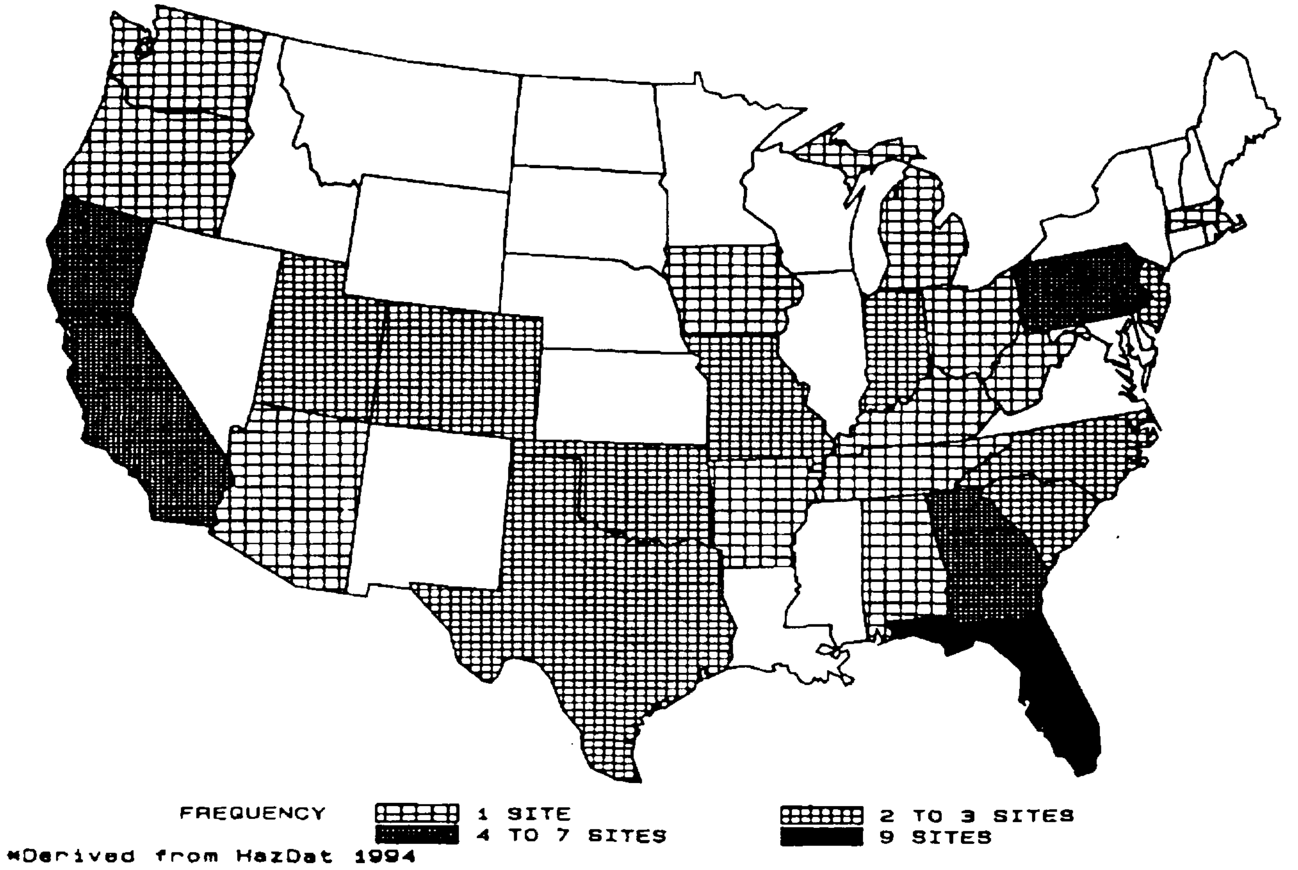
FREQUENCY
1 SITE
4 TO 7 SITES
2 TO 3 SITES
9 SITES
*Derived from HazDat 1994

FIGURE 5-1. FREQUENCY OF NPL SITES WITH TOXAPHENE CONTAMINATION

5.2.1 Air

As a result of its use as an insecticide on cotton in the southern United States, toxaphene was released directly to the atmosphere by aerial and ground application (EPA 1979f). Volatilization of the mixture from treated crop and soil surfaces following application also introduced substantial amounts of toxaphene to the atmosphere. For example, Willis et al. (1980, 1983) substantial amounts of toxaphene to the atmosphere. For example, Willis et al. (1980, 1983) reported volatilization losses from treated cotton canopies of up to 80% of applied toxaphene within 11 days after treatment. Seiber et al. (1979) also reported that volatilization from leaf and soil surfaces was the major removal mechanism for toxaphene applied to cotton crops under field conditions. These investigators reported differential vaporization of the mixture (i.e., selectively greater loss of the more volatile components from soil and leaf surfaces) which was matched by a corresponding enrichment of these components in ambient air samples.

Toxaphene shows a strong tendency to sorb to particulates, and there has been a tendency to believe that toxaphene residuals in older dump sites would be relatively inert. Recent studies, based primarily on theoretical considerations and computer screening models, suggest that, unless a waste site has a clay cap thicker than approximately 0.3 meters, the PCCs could volatilize to the atmosphere. The potential for volatilization increases if the soil matrix in which the toxaphene is buried has a significant sand fraction (Jury et al. 1990). These theoretical findings seem compatible with field measurements on several pesticides (Glotfelty et al. 1989a) that showed the volatilization rates for toxaphene applied to soils were significantly higher than rates for triazine herbicides or alachlor.

5.2.2 Water

Toxaphene has been released to surface waters as a result of its direct application to lakes as a piscicide (EPA 1979f), in waste water releases from manufacturing and formulation plants (Durant and Reimold 1972), and in activities associated with the disposition of residual pesticides. For example, Mirsatari et al. (1987) described the release of aircraft rinse water to drainage ditches following aerial application of toxaphene, and the compound has been detected in surface water samples taken from disposal ponds at a Superfund site (EPA 1986a). Reimold (1974) reported that concentrations in the effluent of a manufacturing plant decreased over a 4-Year period from an average maximum monthly concentration of 2,332 ppb in August 1970 to 6 ppb in July 1974.

Because neat technical toxaphene sorbs to particulates and is markedly hydrophobic, it has been argued that toxaphene would not be able to migrate more than about 10 cm down a soil profile and, therefore, would not be of concern as a groundwater contaminant. Such arguments tend to overlook the fact that technical toxaphene used as a pesticide was usually mixed with a hydrocarbon solvent (e.g., xylene) as a carrier. Especially when such pesticide preparations have been introduced at old waste disposal sites, the toxaphene may be able to move into groundwater with the carrier-solvent. This scenario has been documented at a waste disposal site in California (Jaquess et al. 1989). The authors see this as a possibility at many dump sites containing solvent materials, with toxaphene detections in groundwater at NPL sites in the Mississippi Delta and near Houston, Texas, supporting similar pollution pathways. For most groundwater supplies, however, any significant residence time in poorly oxygenated or anaerobic subsoil vadose zones would be expected to allow for anaerobic biochemical degradation of toxaphene.

5.2.3 Soil

Toxaphene has been released directly to soils mainly as a result of its past use as an insecticide on agricultural crops (EPA 1979f). Disposal of spent livestock-dipping solutions (McLean et al. 1988) and wastes from manufacturing and formulation processes (EPA 1979f) are other significant sources of soil contamination. Mirsatari et al. (1987) reported that toxaphene has been found as a contaminant at pesticide disposal sites at concentrations in soils or sediment approaching or exceeding 100 ppm. Toxaphene was listed as a chemical of concern at the Crystal City Airport Superfund site in Crystal City, Texas. The mixture was detected in surface soil samples taken at the airport following abandonment of agricultural chemicals at the site by defunct aerial application operators (EPA 1987b).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

A combination of monitoring and modeling efforts during the 1980s have firmly established the importance of atmospheric pathways as a major source of PCC inputs to regions in the upper latitudes far removed from regions that had made heavy use of toxaphene as an agricultural pesticide. Adaptations to regional transport models initially developed to study acid rain phenomena show the physical possibility for atmospheric transport of toxaphene from locations in the southern United states to the Great Lakes Region of the northern United States and Canada (Voldner and Schroedere 1989, 1990).

An ongoing series of studies associated with T.F. Bidleman and colleagues in Canada have gathered detailed information on levels of toxaphene in various environmental compartments in regions ranging from the Sargasso Sea to the southeastern United States to various areas in Canada and the Canadian Arctic (Bidleman et al. 1989, 1992, 1993; Cotham and Bidleman 1991; Lockhart et al. 1992; Muir et al. 1990, 1992). These studies help provide at least partial validation for the predictions from regional transport models and document the continued supply of PCC materials to areas in the northern hemisphere far removed from areas of former and significant toxaphene use.

With continued inputs of PCCs from atmospheric pathways, there is the potential for bioaccumulation in food chains. While this does not always pose an exposure risk for human populations, it can be a significant stressor to aquatic organisms and wildlife. Toxaphene, in conjunction with several other organochlorine contaminants, may adversely impact wildlife hormone systems and other reproductive endpoints (Lundholm 1991). This threat is especially pronounced for aquatic mammals that may lack hepatic enzymes found in most terrestrial mammals and enzymes that help metabolize PCC toxicants (Muir et al. 1992). For native American groups in Canada (and possibly Alaska) that hunt aquatic mammals, there are bona fide human health concerns.

Researchers working with the atmospheric transport of toxaphene have assembled useful time series observations for sites along the southern Atlantic coast in the United States, in the

Canadian Maritime provinces, and at stations in the Canadian Arctic (Bidleman et al. 1989, 1992). Comparisons of recent levels in environmental media with baseline concentrations in the 1970s and early 1980s do not suggest declines in toxaphene contaminants, with ambient air concentrations in particular remaining about the same or even increasing Especially in high latitude areas, impacts from toxaphene are still a matter of concern nearly a decade after the United States began phasing out the use of toxaphene as a pesticide agent.

A wide range of values for the vapor pressure of toxaphene has been reported: 0.2-0.4 mmHg at 20°C (Mackinson et al. 1981); 0.4 mm Hg at 25°C (HSDB 1994); $5x10^{-6}$ mmhg at 20°C (Agrochemicals Handbook 1983); $4x10^{-6}$ mmhg at 20°C (Wauchope et al. 1992); $3x10^{-7}$ mmhg at 20°C (Bidleman et al. 1981). The higher vapor pressure values (e.g., 0.2-0.4 mmgh at 20°C) and Henry's law constant (0.21 atm-m^3/mol) for toxaphene suggest that the mixture readily partitions to the atmosphere following release to surface waters and surface soils. The results of numerous field dissipation and atmospheric monitoring studies indicate that the atmosphere is indeed the most important environmental medium for transport of the mixture. In addition to the field dissipation studies (Seiber et al. 1979; Willis et al. 1980, 1983) cited in section 5.2.1, significant partitioning of toxaphene to the atmosphere has been reported in a model agroecosystem study (Nash et al. 1977) and from fallow field soils (Glotfelty et al. 1989a).

The persistence of toxaphene in the atmosphere allows the mixture to be transported long distances from application sites. The presence of toxaphene in surface waters of the Great Lakes has been attributed to aerial transport of the mixture from application sites in the southern United States (EPA 1984b). Detection of toxaphene in the tissues of fish taken from a remote lake on Isle Royale in Lake Superior was also cited as evidence of long-range atmospheric transport (Swackhamer and Hites 1988).

Numerous other investigations have reported long-range atmospheric transport of toxaphene to remote locations. Toxaphene was detected in ambient air samples taken over the western North Atlantic Ocean and Bermuda. The source of the contamination was attributed to cotton-growing areas in the southern United States 1,200 km away (Bidleman and Olney 1975). Maximum concentrations of toxaphene found in North American peat bogs corresponded to the period of maximum production and use of the compound in the United States in the mid-1970s (Rapaport and Eisenreich 1986). The composition of the toxaphene residues in the peat cores indicated that they were delivered to the peat surface by atmospheric transport and deposition with the dominant wind circulation patterns from primary source regions in the southern and southeastern United States. The presence of toxaphene in the following sources has also been attributed to its long-range atmospheric transport: tissues from fish taken from remote lakes in northern Canada (Muir et al. 1988c); fish from pristine areas in the North Atlantic Ocean, North Pacific Ocean, and Antarctic Ocean (Zell and Ballschmier 1980); and fish, birds, and seals from the western North Atlantic Ocean, Arctic Ocean, Greenland, Canada, and Sweden (Andersson et al. 1988).

Evidence of regional-scale transport of the mixture in the drainage basin of the Chesapeake Bay has also been reported (Glotfelty et al. 1988b).

Atmospheric toxaphene is transported back to soil by wet and dry deposition processes

(Glotfelty et al. 1989b; Villeneuve and Cattini 1986). Several investigators have reported that washout in rain appears to be more important than the dry deposition of toxaphene (Bidleman et al. 1981; EPA 1984b). For example, dry deposition accounted for only 15% of the input of atmospheric toxaphene into a rural estuary in South Carolina (Harder et al. 1980).

For higher latitude regions, there is more uncertainty about the importance of specific deposition mechanisms. Especially in Arctic areas, model estimates and available monitoring data (Cotham and Bidleman 1991) suggest that dry particle deposition may be more important than scavenging through snowfall. The mechanisms for toxaphene show many similarities with fate and transport processes for hexachlorobenzene (HCB) and perhaps several other organochlorine toxicants. The hydrophobic properties of these organochlorines encourage partitioning in either a volatile or semi-volatile phase or in forms sorbed to particulates. These properties then facilitate the incorporation of the contaminants into foodchains starting with algae, zooplankton and macroinvertebrates. This in turn encourages biomagnification at higher trophic levels (Cotham and Bidleman 1991; Hargrave et al. 1992).

The high K^{oc} (soil organic carbon partition coefficient) value for toxaphene suggests that the mixture should be strongly sorbed to soil particulates and therefore should be relatively immobile to leaching and inhibited from volatilizing from subsurface soils. Field studies have verified this behavior. Half-lives ranging from approximately 1 to 14 years have been reported for toxaphene in soils. In surface soils, where volatilization will be a significant partitioning process, half-lives of 2 months and 4 months have been reported for samples taken at the top 2.5 cm and top 7.5 cm, respectively (Sieber et al. 1979). Between 85 and 90% of the total toxaphene residues were found in the upper 23 cm (i.e., cultivated layer) of a sandy loam test soil 13 years after the last foliar application of the mixture (Nash and Woolson 1968). Following multiple annual applications of toxaphene to cotton crops grown in a clay soil, Swoboda et al. (1971) detected 90-95% of toxaphene residues in the top foot of the 5-foot profile sampled; toxaphene was not detected in any of the drainage water samples taken from the site. About 93% of the toxaphene found in runoff from a treated cotton field on a silty clay soil was bound to the sediment fraction; only 7% was found in the aqueous fraction of the runoff (McDowell et al. 1981). Toxaphene concentrations in runoff varied seasonally, and losses in two of the years studied totaled only 0.5-1% of the amount applied. Runoff losses from a cotton crop grown in the Mississippi Delta were found to be 0.4% of applied toxaphene (Lorber and Mulkey 1982). According to the simulation models Foliar Washoff of Pesticides (FWOP), Chemical Runoff and Erosion from Agricultural Management Systems (CREAMS), and Pesticide Runoff Simulator (PRS), up to 3% of applied toxaphene may be lost in runoff from treated agricultural fields; all of the toxaphene would be associated with the sediment fractions (Smith and Carsel 1984). However, the mobility of toxaphene in soils is influenced by soil moisture status and the presence of other organic solvating materials (Jaquess et al. 1989). Toxaphene did leach from laboratory columns of sand and sandy loam soils treated with organic solvents and emulsifiers when the columns were allowed to dry completely between wetting cycles. The mixture did not leach from the amended columns when a similar amount of water was applied on a continuous basis. Drying of the soil allowed crevices to form in the columns which expedited movement of the mixture. Toxaphene dissolved in the organic solvent or contained in the emulsifier amendment could leach through the macropores.

There is also evidence that vaporization is the primary route of loss from toxaphene-treated foliage. In a study by Seiber et al. (1979), residues of toxaphene were analyzed in cotton leaves and associated air samples up to 58 days after application (9 kg/ha) to a cotton field in the San Joaquin Valley, California. Analyses of the cotton leaf samples indicated a 59% loss of toxaphene at 28 days after application. Leaf residues declined from 661 ppm on the day of application to 135 ppm on day 50 after application, with an observed trend toward greater loss of the more highly volatile components. A corresponding enrichment of volatile toxaphene components was observed in air samples. There was no indication of chemical degradation in these samples in spite of the presence of abundant sunlight, oxygen, and atmospheric oxidant throughout the study.

Toxaphene in surface waters that is not volatilized to the atmosphere is sorbed to sediments or suspended particulates, which are ultimately deposited in sediments (EPA 1979a). The lower-solubility, more-chlorinated components of the mixture are preferentially sorbed to particulates and sediments. Paris et al. (1977) reported that the less soluble, more highly chlorinated fractions of toxaphene also appear to be selectively sorbed to aquatic microorganisms and, consequently, would be expected to bioaccumulate up the food chain. At very low concentrations, sorption of toxaphene to aquatic microorganisms may be described adequately by the following relationship:

Cd = Cm/Cw

Where

Cd = distribution coefficient (unitless)

Cm = mg toxaphene sorbed/mg microorganism

Cw = concentration of toxaphene in the medium (mg/mg) at equilibrium.

Cd values ranged from 3.4x10^{3} to 1.7x^{4} for a variety of bacteria, fungi and algae *(Bacillus subtilis, Flavobacterium harrisonii, Aspergillus sp., Chlorella pyrenoidosa)* (Paris et al. 1977). Direct sorption of toxaphene onto sediment, plankton, and other suspended solids deposited in the sediment has also been reported in three lakes in Wisconsin where the mixture was applied for the control of nongame fish. Toxaphene sorbed to sediments was not found to be readily desorbed (Veith and Lee 1971).

Toxaphene is bioconcentrated in the tissues of aquatic organisms. In a flow-through bioassay conducted with the long-nose Killifish *(Fundulus similis),* bioconcentration factors (BCF = concentration in tissue/concentration in test medium) of up to 33,300 in fry and 60,000 in juvenile fish after 28 days of exposure were reported; BCFs in adults ranged from 4,200 to 6,800 after 14 days of exposure (Schimmel et al. 1977). Oysters *(Crassostrea virginica)* exposed to 1 ppb toxaphene have been found to accumulate up to 23 ppm in tissue after 24 weeks exposure; tissue concentrations decreased to nondetectable levels at the end of a 12-week depuration period (Lowe et al. 1971). In a model ecosystem study using radiolabeled toxaphene, BCFs of 6,902 for algae, 0.600 for snails, 890 for mosquitoes, and 4,247 for fish

(Gambusia affinis) were reported (Sanborn et al. 1976). Toxaphene has also been detected in the tissues of aquatic organisms in numerous field studies (see Section 5.4.4). For example, mean toxaphene concentrations of 11 ppm lipid tissue for lake trout *(Salvelinus namaycush)* and 7 ppm lipid tissue for whitefish *(Coregonus clupeaformis)* taken form a remote lake on Isle Royale in Lake Superior have been reported (Swackhamer and Hites 1988).

Toxaphene also appears to be biomagnified in aquatic food chains, although not to the extent of other chlorinated insecticides, such as DDT. For example, Evans et al. (1991) reported trophic biomagnification of toxaphene, with toxaphene concentration increasing by an average factor of 4.7 from plankton (mean concentration = 0.55 ppm) to fish (deepwater sculpin: mean concentration = 2.57 ppm). DDE and PCBs were found to be more strongly biomagnified, increasing 28.7 and 12.9 times, respectively, in average concentration from plankton to sculpin. In a study that included analyses of tissue residue levels in 16 species of fish, birds, amphibians, and reptiles, biomagnification of toxaphene was reported in three oxbow lakes in northeastern Louisiana (Neithammer et al. 1984). Tissue residue concentrations were highest in tertiary consumers (carnivores) and lowest in primary consumers (herbivores); toxaphene was not detected in the limited number of surface water or sediment samples taken from the lakes. The source of the toxaphene was apparently the surrounding cotton and soybean cropland, which had historically received heavy pesticide applications. Biomagnification was also reported in a study that included analyses of tissue residue levels in 8 species of fish and water snakes in the area of the Yazoo National Wildlife Refuge, Mississippi (Ford and Hill 1991). Biomagnification of several organochlorine pesticides, including toxaphene, was apparent from soil sediments (geometric mean concentration approximately 0.1 ppm) to mosquito fish, a larger secondary consumer and forage fish (geometric mean concentration = 0.25 ppm) to the spotted gar, a tertiary consumer (geometric mean concentration = 2.71 ppm). There was, however, no clear pattern of biomagnification in larger secondary consumers such as smallmouth buffalo and carp, or in tertiary consumers such as water snakes.

In contrast, no biomagnification of toxaphene in a Canadian arctic marine food chain was reported in another study (Muir et al. 1988a). Toxaphene was detected in the muscle tissue of the arctic cod *(Boreogadus saida)* at a mean concentration of 0.018 ppm but not in the blubber and liver of the ringed seal *(Phoca hispida)*, which preys on the cod, or the fat of the polar bear *(Ursus maritimus)*, which preys on the seal. In a separate study, toxaphene was found in the tissues of white-beaked dolphins *(Lagenorhynchus albirostrics)* and pilot whales *(Globicephala melaena)* taken off the coast of Newfoundland in 1980 and 1982 (Muir et al. 1988b). The toxaphene peaks from the gas liquid chromatography (GLC) analyses of the dolphin blubber indicated considerable metabolism of the mixture, as compared with toxaphene residues detected in the local fish populations preyed upon by the dolphins. Other studies in Canada around Baffin Bay have found cetacean blubber with an average toxaphene congener concentration of 9.2 ppm for male narwhals. Tissue concentrations in individual males ranged up to 13.2 ppm (Muir et al. 1992). Andersson et al. (1988) performed some limited sampling of biota from various trophic levels in marine food chains in the western North Atlantic Ocean, Greenland, Sweden, and Canada. They reported that toxaphene concentrations in fish, bird, and seal tissues ranged from 0.33 to 17 ppm fat tissue for all trophic levels versus 0.14-990 ppm for DDT and PCB residues. These results were interpreted as being indicative of less biomagnification and/or more effective metabolism of toxaphene at higher trophic levels, as compared with DDT and PCB.

5.3.2. Transformation and Degradation

5.3.2.1 Air

Direct photolytic degradation of toxaphene in the troposphere apparently does not occur. No information was found regarding the susceptibility of toxaphene to free radical oxidation in the atmosphere. The worldwide, long-range atmospheric transport of the mixture suggests that toxaphene is relatively resistant to transformation in the atmosphere. Since the production of toxaphene involves exposing chlorinated camphenes to UV-radiation, the congeners in the final mixture are resistant to degradation from direct photolysis (EPA 1976a; Korte et al. 1979). Rapaport and Eisenreich (1986) cited an atmospheric residence time of 46-70 days for the mixture. They noted that the toxaphene found in peat cores taken from remote regions in the northern United States and Canada was deposited from the atmosphere in a relatively untransformed state.

5.3.2.2 Water

Toxaphene is resistant to chemical and biological transformation in aerobic surface waters. It is not expected to undergo direct photolysis or photooxidation (EPA 1979a). Hydrolysis is also not an important fate process; a hydrolytic half-life of greater than 10 years for pH 5 to 8 and 25°C has been estimated (EPA 1976d).

A factor complicating the analysis of fate and transport processes in aquatic systems is the difficulty in making trend comparisons for monitoring information collected before the early 1980s. Reliable detection of low levels of PCCs became possible only with the adoption of capillary column gas chromatography (GC) technology in the early 1980s. The prevailing earlier packed-column methods were usually unable to provide reliable total toxaphene readings for the large numbers of congeners (each present in minute amounts) encountered in most samples (Schmitt et al. 1990).

For instance, U.S. Fish and Wildlife Service programs like the National Pesticide Monitoring Program (now the National Contaminant Biomonitoring Program) started in the 1970s; however, due to problems in quantification with the older technologies results of these programs cannot be compared with modern toxaphene sampling results (Schmitt et al. 1990). These problems seriously interfere with drawing conclusions for such media as sediments or tissue samples, and make it almost impossible to make trend determinations for ambient water.

Another complicating factor is mounting evidence that wastes from paper and pulp operations may be a source of toxaphene-like materials. Much of this research comes from countries where toxaphene was never used as a pesticide agent but where anomalous findings of PCC materials were encountered. There is a tendency in such cases to conclude that all the PCC congeners are the result of hemispheric or global atmospheric transport pathways, but in some cases, PCC from paper and pulp wastes may help explain localized hotspots. While most of this research has come from foreign countries (Jamuzi et al. 1992), the State of Michigan (EPA 1993a) is confident that PCC congeners from paper industry wastes are found in the Great Lakes region.

5.3.2.3 Sediment and Soil

Toxaphene has been reported to be quite persistent in aerobic surface soils. Nash and Woolson (1967) reported a half-life of 11 years in an aerobic sand loam soil that had received high application rates (112 and 224 kg/ha, corresponding to approximately 50 and 100 ppm) of toxaphene. Seiber et al. (1979) reported half-lives of approximately 2 months (top 2.5 cm) and 4 months (top 7.5 cm) from aerated topsoil that had been treated with toxaphene at an application rate of 9 kg/ha. While the observed declines in toxaphene concentrations were primarily due to vaporization, at least one toxaphene component was reported to be significantly degraded. The mechanism of degradation was postulated to be dehydrochlorination or reductive chlorination, but this was not investigated further. Studies by Parr and Smith (1976) and Smith and Willis (1978) in a silty loam soil indicated no transformation of toxaphene in moist amended (i.e., alfalfa meal added) or unamended samples incubated under aerobic conditions, but rapid transformation (65-96% over 4 weeks) in amended and unamended samples incubated under anaerobic conditions. The transformation was reported to be a dechlorination reaction. No transformation was observed in autoclaved samples.

There is conflicting information in the literature regarding the transformation of toxaphene in sediments. Seiber et al. (1979) found that in sediment samples taken from the bottom of a drainage ditch a year or more after application of toxaphene to an adjacent field (13.5 kg/ha), several major components of toxaphene, including toxicant B, were significantly degraded. Reductive dechlorination appeared to be a major mechanism of degradation. This mechanism results in lower weight products than occur in technical toxaphene, at least some of which are relatively stable in the environment. As a consequence, the authors emphasized that the environmental and toxicological significance of these products needs to be determined. Williams and Bidleman (1978) reported that toxaphene transformation in an anaerobic salt marsh sediment was mediated chemically, rather than biologically, in microcosm studies. The transformation, believed to be a reductive dechlorination, was rapid, occurring within 2-6 days even in sterilized samples. In contrast, Mirsatari et al. (1987) found no transformation of toxaphene in autoclaved (i.e., sterile) sediment and soil samples over a 60-day test period. In addition, no transformation was observed in unsterile sediment samples incubated under aerobic conditions for 6 weeks. Rapid transformation (half-life = 1 week) was observed only in unsterile sediment samples amended with organic matter and incubated under anaerobic conditions. The microbially mediated transformation was apparently a reductive dechlorination. Clark and Matsumura (1979) added radiolabeled toxaphene to sediments and incubated them for 30 days under aerobic and anaerobic conditions. As in the Mirsatari et al. (1987) study, no transformation was observed in autoclaved samples. However, toxaphene was transformed in the aerobically incubated samples by the bacterium *Pseudomonas putida.* Clark and Matsumura (1979) stated that toxaphene biotransformation is likely to proceed initially as a dechlorination reaction under anaerobic conditions followed by oxidative transformation of the less chlorinated products under aerobic conditions. Thus, toxaphene apparently undergoes some biotransformation in the sediment layers of rivers and lakes under both anaerobic and aerobic conditions.

There is a limited amount of literature dealing with sediment monitoring of toxaphene. Since it is fairly volatile, materials reaching sediments would be expected to volatize over time periods in the neighborhood of days. Residual amounts would then be expected to become partitioned into food chains or decomposed under anoxic conditions if they migrated into deeper sediment layers. Studies in the Mississippi Delta documented the absence of toxaphene in anaerobic wetland sediments (Cooper 1991).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

As a result of past widespread use as an insecticide and its persistence, toxaphene has been detected in ambient air, surface and groundwater, soils and sediments, rainwater, and food. Data reported in this section have been obtained largely from national surveys in an attempt to present a representative national perspective of toxaphene contamination of various environmental media. However, the reader should note that toxaphene contamination of certain media may be a more serious problem on a regional basis than indicated by these national averages. For example, higher soil concentration levels can be expected in cotton growing areas of the South, and higher tissue residue levels have been found in fish taken from the Great Lakes.

5.4.1 Air

Toxaphene has been detected in ambient air and rainwater samples collected at a number of sites in the United States; however, the available data are not current. In an ambient air monitoring study conducted at 4 urban sites (Baltimore, Maryland; Fresno, California; Riverside, California; and Salt Lake City, Utah) and at 5 rural sites (Buffalo, New York; Dothan, Alabama; Iowa City, Iowa; Orlando, Florida; and Stoneville, Mississippi) in the United States in 1967-1968, toxaphene was detected only in samples taken from three agricultural areas in southern states. Maximum concentrations detected were 68 ng/m^3 (detected in 11 of 90 samples), 2,520 ng/m^3 (9 of 99 samples), and 1,340 ng/m^3 (55 of 98 samples) in Dothan, Alabama; Orlando, Florida; and Stoneville, Mississippi, respectively (Stanley et al. 1971). Toxaphene was included in the ambient air sampling of agricultural and urban areas conducted in 14-16 states as part of the National Air Pesticide Monitoring Program. For the years 1970-1972, toxaphene was detected in 3.5% of the 2,479 samples collected at mean and maximum concentrations of 17 ng/m^3 and 8,700 ng/m^3, respectively; and the mean of the positive samples was 1,890 ng/m^3 (Kutz et al. 1976). In 1981, toxaphene was detected at maximum concentrations of 9.05 ng/m^3, 1.73 ng/m^3, 0.44 ng/m^3, and 0.14 ng/m^3 in Greenville, Mississippi; Saint Louis, Missouri; Bridgeman, Michigan; and Beaver Island, Michigan; respectively (EPA 1984b; Rice et al. 1986).

A seasonal variation in toxaphene concentrations in ambient air samples collected in Stoneville, Mississippi, from 1972 to 1974 was noted in a study by Arthur et al. (1976). The highest concentrations were observed in summer months, corresponding to the growing season, and the lowest in winter months. The sampling site was located in the middle of the most intensive cotton-growing area in Mississippi. The maximum concentration detected in weekly air samples was 1,747 ng/m^3. Average monthly levels were 258,82, and 160 ng/m^3 for 1972, 1973, and 1974, respectively.

Toxaphene has also been detected in ambient air samples taken at remote locations. Toxaphene concentrations of less than 0.04-1.6 ng/m^3 in ambient air samples taken over the western North Atlantic Ocean from 1973 to 1974 have been reported (Bidleman and Olney 1975). Mean concentrations in ambient air samples from Bermuda were 0.81 ng/m^3 (±0.45 ng/m^3 S.D.) and 0.72 ng/m^3 (±0.09 ng/m^3 S.D.). Toxaphene was detected in rainwater samples taken in southern France near the Mediterranean Sea at mean concentrations of 7.2 ppt (range: not detected-53 ppt) and 25.2 ppt (range: not detected-81 ppt) in solution and sorbed to particulates, respectively (Villeneuve and Cattini 1986).

5.4.2 Water

The median toxaphene concentration in ambient surface waters in the United States in 1980-1982, according to analyses of EPA's STORET water quality database, was 0.05 ppb (Staples et al. 1985). The mixture was detected in 32% of the 7,325 samples collected over that period. Toxaphene was detected in only 3.4% of the 708 effluent samples taken during 1980-1983 at a median concentration of less than 0.2 ppb.

In a study of toxaphene concentrations in surface water and runoff from the Bear Creek, Mississippi, watershed conducted in 1976-1979, toxaphene concentrations in surface water were found to be measurable only after major runoff events (Cooper et al. 1987). At other times, only trace amounts of the compound (<0.01-1.07 ppb) were detected. However, runoff from two fields historically cultivated in cotton and soybeans contained toxaphene residues of 0.04-4.18 ppb and 289-2,964 ppm in the aqueous and particulate fractions, respectively. In contrast, toxaphene was not detected in 86 samples of municipal runoff collected from 15 cities in the United States in 1982 as part of the Nationwide Urban Runoff Program (Cole et al. 1984).

Toxaphene was detected in surface water samples taken from 2 of 9 disposal ponds at a Superfund site at maximum concentrations of 17 ppb for surface water (EPA 1986a).

A study of the chemical composition of leachates within existing landfills, reported that toxaphene was not detected in any of the municipal landfill leachates examined (Brown and Donnelly 1988). However, the mixture was detected in industrial landfill leachates at a concentration of ≤10 ppb.

No current information was found in the literature regarding toxaphene contamination of drinking water supplies. Toxaphene concentration ranged from 5 to 410 ppt in drinking water samples collected in Flint Creek, Alabama, between 1959 and 1963 (Faust and Suffet 1966).

In a review of groundwater monitoring data collected in 1981-1984 from more than 500 wells at

334 hazardous waste disposal sites (RCRA and CERCLA sites) located in all 10 EPA regions and 42 states, Plumb (1987) reported that toxaphene was detected at 0.2% frequency at the 178 CERCLA sites examined and at 1.1% frequency at the 156 RCRA sites examined. Concentration data were not provided.

5.4.3 Sediment and Soil

Toxaphene has been detected in some samples of urban and agricultural soils from throughout the United States. Wiersma et al. (1972a) detected the mixture in concentrations that ranged from 0.11 to 52.7 ppm in samples of surface soils from 3 of 8 U.S. cities in 1969. In another study of 14 cities conducted in 1970, toxaphene was detected at 3 of 28 sites (10.7%) at mean and geometric mean concentrations of 1.94 ppm and 0.012 ppm, respectively; concentrations in the positive samples ranged from 7.73 to 33.4 ppm. In Sikeston, Missouri, toxaphene was detected at 1 of 27 sites at a concentration of 0.60 ppm. Carey et al. (1979a) monitored soils in 5 U.S. cities in 1971 and found toxaphene only in 11 of 43 samples (25.6%) taken from Macon, Georgia, at a mean concentration of 0.24 ppm (range, 0.23-4.95 ppm; geometric mean, 0.02 ppm).

Toxaphene residues in domestic cropland soils were surveyed in the National Soils Monitoring Program (Carey et al. 1978, 1979b; Wiersma et al. 1972b). Rapaport and Eisenreich (1986) found toxaphene in samples of peat from bogs located in remote regions of the northern United States and Canada at concentrations ranging from less than 1 ppb (detection limit) to 30 ppb.

Toxaphene has also been detected in sediment samples, primarily in the southern United States. Toxaphene was detected in 2.2% of 548 sediment samples collected in the lower Mississippi River and its tributaries in 1964 and from 1966 to 1967. Concentrations in the positive samples ranged from 0.1 to 13.18 ppm, the mean concentration was 6.5 ppm (Barthel et al. 1969). In southern Florida, toxaphene was detected, but not quantified, in 3.2% of 126 sediment samples collected from 1969 to 1972 (Mattraw 1975). In 27 sediment samples collected in Delaware and in the Raritan Canal, New Jersey, from 1979 to 1980, toxaphene was not detected (Granshrom et al. 1984). At a site 1.4 miles from the outfall of a toxaphene plant on Terry Creek in Brunswick, Georgia, toxaphene was found at a concentration of 5.27 ppm in a 70-80 cm sediment sample collected in 1971 (IARC 1979). According to analyses of EPA's STORET water quality database, the median toxaphene concentration in sediment was 2.0 ppb; the compound was detected in 25% of the 1,603 samples taken during 1980-1983 (Staples et al. 1985). Toxaphene was also detected in sediment samples taken from 2 of 9 disposal ponds at a Superfund site at a maximum concentration of 2,900 ppb (EPA 1986a).

In a recent investigation of organochlorine pesticides in soil sediments in the upper Steele Bayou watershed of Mississippi, toxaphene was found in 41% of 56 samples collected at two depths (2.54- 7.62 cm and 25.4-30.48 cm) along 8 different drainages (Ford and Hill 1991). The geometric mean and maximum wet weight toxaphene concentrations were 0.12 ppm and 2.80 ppm for upper samples, and 0.07 ppm and 4.60 ppm for lower samples, respectively. There was no significant difference in toxaphene concentrations between corresponding upper and lower samples.

Ongoing studies in agricultural areas of the Mississippi Delta provide indications of the persistence of toxaphene in soils and sediments under what might be construed as a worst case scenario. Results of investigations at Moon Lake and sites within its watershed just to the east of the main levees on the Mississippi River in Coahoma County, Mississippi, have been reported (Cooper 1991). In soils, which provide a generally aerobic redox environment, the average total toxaphene level based on 69 samples collected in the period 1983-1984 was 734 ppb. Sediments in the lake averaged 12.4 ppb. In core samples from wetland flats displaying marked signs of anaerobic conditions, there was no detectable toxaphene. These findings underscore that it is only in media providing appreciable residence times in biologically active anoxic conditions that one can expect significant biochemical degradation of toxaphene. In even moderately aerobic environments, and especially in soil or sediments rich in clay colloids, the pesticide agent is persistent for many years.

5.4.4 Other Environmental Media

Levels of toxaphene in food have been determined as part of FDA's Total Diet Studies. In a 1980-1982 survey of pesticides, toxaphene was detected in samples of food groups that comprised typical infant and toddler diets. Concentrations ranging from 0.1 to 0.2 ppm (number positive samples = 3) and from 0.7 to 0.12 ppm (number positive samples = 6) were found in the oils and fats food groups of infants' and toddlers' diets, respectively. The samples were collected in 13 U.S. cities. Toxaphene was not detected in drinking water or the other foods examined in the diet of either group. Other food groups examined included: whole milk; other dairy and dairy substitutes; meat, fish, and poultry; grain and cereal products; potatoes; vegetables; fruit and fruit juices; sugar and adjuncts; and beverages (Gartrell et al. 1986a, 1986b).

In more recent FDA Total Diet Studies, the frequency of occurrence of toxaphene detections was 1% in 1989 (FDA 1990), 2% in 1990 (FDA 1991), and <1% in 1991 (FDA 1992). Estimated toxaphene intakes were less than 0.01 μg/kg body weight/day for 6--11-month-old infants, 14--16-year-old males, and 60--65-year-old females during this period, with a noticeable downward trend from 1989 to 1991 in all age categories (see Section 5.5 for more detailed information on estimated daily toxaphene intakes). While progressive improvements in analytical technologies complicate comparisons of older values with more recent collections, the FDA Total Diet Studies clearly suggest that general population intake levels have fallen dramatically over the last decade.

A regional food basket study conducted in San Antonio, Texas, in the period from 1989 to 1991 screened 6970 produce items for a suite of 111 pesticide analytes. Toxaphene was not encountered on any produce items at levels above FDA violation thresholds (Schattenberg and Hsu 1992).

Toxaphene was found in a National Pesticide Monitoring Program survey of estuarine molluscs conducted from 1965-1972 (Butler 1973). Toxaphene was found at maximum concentrations of 11 ppm in samples from California (4 positives in 85 samples) and 54 ppm in samples from Georgia (128 positives in 211 samples).

Georgia (128 positives in 211 samples).

Residues of toxaphene and other pesticides were examined as part of the National Contaminant Biomonitoring Program (NCBP, formerly a part of the National Pesticide Monitoring Program) conducted in 1984. Composite samples (N=321) of bottom-feeding and predatory fish were taken from 112 stations located along the major domestic rivers and in the Great Lakes. Toxaphene residues were detected in fish tissue samples collected at 69% of the stations. In earlier sampling periods, the percentage of stations where detectable residues were present was approximately 60% (1976-77 and 1978-79) and 88% (1980-81). The maximum and geometric mean wet weight concentrations of the mixture in the samples were 8.2 ppm and 0.14 ppm, respectively, the lowest values found in any NCBP sampling period. Maximum and geometric mean wet weight concentration data for earlier sampling periods were 12.7 ppm and 0.34 ppm (1976-77), 18.7 ppm and 0.28 ppm (1978-79), and 21.0 ppm and 0.28 ppm (1980-81), respectively (Schmitt et al. 1985, 1990).

Toxaphene concentrations in nearshore fish collected from the mouths of rivers and embayments around Lake Michigan in 1983 were determined in a study conducted by Camanzo et al. (1987). In 28 composite whole-fish samples collected from 14 sites, toxaphene was detected at a mean concentration of 0.04-3.46 ppm in samples of rock bass, northern pike, common carp, smallmouth bass, lake trout, bowfin, pumpkinseed, channel catfish, and largemouth bass. The investigators note that bottom-feeding species (e.g., common carp, channel catfish) had higher residue levels than top predatory fish (e.g., northern pike), possibly as a result of the bottom-feeders being older, having more fat tissue, and living in proximity to contaminated sediments. Most of the residues differed from the GLC peaks for the toxaphene standard, indicating that some metabolism/transformation of the compound had taken place.

Toxaphene was also detected in tissue samples from 7 species of aquatic animals in the area of the Yazoo National Wildlife Refuge, Mississippi collected during 1988 (Ford and Hill 1991). Results of this study are summarized below.

Species	Number of Samples	Geometric Mean Concentration (ppm wet weight)	Concentration Range (ppm wet weight)
Mosquitofish	25	0.25	ND - 0.25 (17)[a]
Carp	8	3.06	0.51 - 6.20 (8)

Smallmouth buffalo	6	5.77	0.75 - 15.00 (6)
Bowfin	5	2.70	0.27 - 8.60 (5)
Spotted gar	10	2.71	ND - 16.00 (9)
Water snakes	20	0.33	ND - 27.00 (17)
Cotton mouths	10	0.03	ND - 1.30 (5)

ND = not detected (minimum detection limit 0.01 ppm)

[a] Numbers in parentheses indicate numbers of samples containing toxaphene.

The authors noted that the occurrence of toxaphene levels above the FDA limit of 5.0 ppm in fish was a cause for public health concern.

Toxaphene concentrations of 1.1 ppm on a wet weight basis (24 ppm fat weight basis) in cod liver samples and 0.4-1.0 ppm wet weight basis (4.4-12 ppm fat weight basis) in herring fillets collected from the east coast of Canada were reported by Musial and Uthe (1983). Toxaphene was not detected in samples of deep sea scallops.

The chief regions where bioaccumulation or biomagnification in fish or wildlife might pose a serious public health concern are in high latitude areas outside the contiguous United States. Studies on marine mammals in Canada (Muir et al. 1992) suggest risks to Native American groups that eat blubber or visceral tissues such as liver. While no comparable work has been done in Alaska, this is an area of the United States where there could be genuine concern for Eskimo hunters that still consume marine mammals.

Within the contiguous United States, there is concern for populations that regularly consume meat from omnivores or carnivores, such as raccoons. Studies reported in Ford and Hill (1990) on the Upper Steele Bayou near the Yazoo National Wildlife Refuge in Mississippi show wildlife still displaying toxaphene residues in adipose tissues in collections made in 1988. The residues were most pronounced for raccoons, where adipose concentrations of total toxaphene up to 31 ppm (weight mass basis) were observed. The Upper Steel Bayou region in Washington County was close to another area on the Big Sunflower River previously studied in 1980. Due to radical changes in the GC methods for analyzing toxaphene, researchers are hesitant to make comparisons emphasizing numeric concentration levels (Ford and Hill 1990). Still, in the late 1970s, the U.S. Fish and Wildlife Service was concerned enough to issue advisories on human consumption of wildlife in the Mississippi Delta region. Many members of this region's poor, rural population eat significant amounts of game meat, including raccoons.

Fillets of Great Lakes coho salmon collected from the 5 lakes in 1980 had mean concentrations of 0.19-1.53 ppm of "apparent toxaphene" (Clark et al. 1984). Lake trout collected from Lake Michigan have been found to contain residues of toxicant congeners A and B that were approximately one-tenth or less of the estimated total toxaphene residues (Gooch and Matsumura 1985, 1987). The percentages of toxicant A and toxicant B in the fish residues were, however, similar to those in the technical toxaphene, indicating that in the environment the rates of degradation of these congeners are roughly the same as those of other toxaphene components.

Toxaphene was also reported to be a contaminant of tobacco crops and products. Gibson et al. (1974) reported that toxaphene was a sporadic contaminant of Kentucky Burley tobacco crops during the period 1963-1972. Toxaphene was detected in about 4% of the samples at maximum concentrations exceeding 100 ppm. Toxaphene was also detected in 6 brands of cigar tobacco sampled in 1972 at an average concentration of 0.92 ppm; four of the six samples had toxaphene concentrations of less than 0.5 ppm.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Current human exposure to toxaphene in the United State appears to be very limited. A summary of results from the FOODCONTAM database (Minyard and Roberts 1991) for the period 1988-1989 showed no detectable toxaphene residues in food samples. This database involves 10 states that follow QA/QC protocols in line with those of such federal counterpart agencies as the USDA, EPA and the FDA. Members of the general population may be exposed to low levels of the mixture through ingestion of contaminated foodstuffs and possibly through inhalation of ambient air (Kutz et al. 1991). Populations consuming large quantities of fish and shellfish potentially contaminated with toxaphene may be exposed to higher levels than the general public. Exposure to higher concentrations of toxaphene may also result from contact with contaminated media in the vicinity of waste disposal sites containing toxaphene-contaminated wastes. No information was found in the available literature regarding the size of the human population potentially exposed to toxaphene in the vicinity of hazardous waste sites.

Based on the toxaphene levels in their 1980-1982 food survey, the FDA estimated average dietary intakes, in ug/kg body weight/day of 0.080, 0.036, and 0.023 for infants, toddlers, and adults, respectively (Gartrell et al. 1986a, 1986b). However, actual intakes must be lower than the estimates because other reported average dietary intakes were based on the mean concentration of the positive samples. More recently, toxaphene intakes, in µg/kg body weight/day, estimated for the total diet analyses were 0.0059, 0.0087, and 0.0046 in 1989 (FDA 1990); 0.0071, 0.0085, and 0.0093 in 1990 (FDA 1991); and 0.0033, 0.0059. and 0.0024 in 1991 (FDA 1992) for 6-11-month-old infants, 14-16-year-old males, and 60-65-year-old females, respectively. These dietary intake estimates suggest a decreasing trend following the cancellation of most registered uses of toxaphene as an agricultural pesticide in the United

States in 1982 and a cancellation of all registered uses in 1990.

In contrast, average daily inhalation exposures are likely to be much less than dietary exposures. Inhalation exposure to the mixture has been estimated to be 0.0004-0.0033 μg/ day (HSDB 1994, average daily air intake estimated based on ambient air concentrations in the range of 0.02-3.3 ng/m^3.

Toxaphene has not been detected in human adipose tissue. However, it has been detected at a concentration of 0.1 mg/kg on a milk fat basis in pooled human breast milk samples collected in Uppsala, Sweden, (Vaz and Blomkvist 1985); however, similar data on U.S. populations are not available.

When toxaphene was being manufactured and used as an insecticide, occupational exposure to toxaphene, particularly via the dermal and inhalation routes, may have been significant. Dermal exposures of 22.72 and 16.56 μg/hour were reported by Munn et al. (1985) for adults and youths, respectively, harvesting a toxaphene-treated onion crop in the Platte River Valley of Colorado in 1982. Any farmers or pesticide applicators who formerly used the mixture to control insects on livestock and crops may have been exposed to relatively high concentrations via these exposure routes.

According to OSHA (1991), the current 8-hour time-weighted average (TWA) permissible exposure level for toxaphene is 0.5 mg/m^3 in workplace air. The exposure limit recommended by NIOSH is the lowest feasible concentration (NIOSH 1992).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Members of the general population currently having potentially high exposures to toxaphene include populations (e.g., recreational or subsistence fishermen) which consume large quantities of fish and shellfish obtained from waterbodies where fish consumption advisories for toxaphene contamination are in effect and residents living near the 58 NPL sites known to be contaminated with toxaphene. No information was found in the available literature regarding the size of these populations. The concentrations of toxaphene in all of the contaminated media to which these populations might be exposed have not been adequately characterized.

In high latitude Scandinavian countries, there are documented cases of toxaphene-congeners in fats from human breast milk (Mussalo-Rauhamaa et al. 1988; Vaz and Blomkvist 1985). Estimates of risks to nursing infants are complicated since the identified congeners were usually partially metabolized and there is little information on the toxicities of such congeners.

As noted above in Section 5.4.4, there could be risks of high exposures for two types of subpopulations that consume large amounts of marine mammals or game animals. These include Native American groups in Alaska, although any quantification of the risks would have to be based on data collected from such groups as the Inuit in the Baffin Bay area of Canada (Muir et al. 1992). The other subpopulation with potentially high exposures would be the rural poor in parts of the Southeast where historically heavy use of toxaphene as a pesticide agent occurred. Where such families eat large amounts of hunted game animals, and particularly where they might consume such species as raccoons, there could be higher exposure risks (Ford and Hill 1990).

In other parts of the United States, there may be localized concerns over exposure from consuming fish or shellfish. As of September 30, 1993, toxaphene was cited as the causative pollutant in four fish consumption advisories in two southwestern states (Arizona and Texas) (RTI 1993). The advisories are summarized below:

State	Waterbody	Extent
Arizona	Gila River	From above confluence with Salt River and SW to Painted Rocks Borrow Pit lake near Gila Bend
Arizona	Hassayampa River	From Buckeye Canal to the Gila River
Arizona	Salt River	Below or west of 59th Avenue in Phoenix
Texas	Arroyo Colorado	Above Port of Harlingen (Willacy, Cameron, and Hidalgo Co.)

EPA has identified toxaphene as a target analyte and recommended that this chemical be monitored in fish and shellfish tissue samples collected as part of state toxics monitoring programs. Residue data obtained from these monitoring programs should be used by states to conduct risk assessments to determine the need for issuing fish and shellfish consumption advisories (EPA 1993a).

In much of the contiguous United States where toxaphene was once used as a pesticide agent, however, the incidence of toxaphene residues in freshwater fish does seem to be declining. While changes in GC analysis technologies make it very hard to compare post-1980 records with analyses conducted in the 1970s, results from two sampling periods in the 1980s from the U.S. Fish and Wildlife Service National Contaminant Biomonitoring Program show that the number of sites with detectable levels of total toxaphene in fish tissue samples dropped from 88% in 1980-1981 to 69% in samples collected in 1984. This is interpreted as an indication of a declining trend in toxaphene contamination levels in fish in the contiguous United States (Schmitt et al. 1990).

5.7 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of toxaphene is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of toxaphene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Identification of Data Needs

Physical and Chemical Properties. In general, physical and chemical properties of toxaphene have been sufficiently well characterized to permit estimation of its potential environmental fate (Bidleman et al. 1981; Mabey 1981a; Mackison et al. 1981; Merck 1989; Worthing 1979). However, values for vapor pressure ranging from 3x10^{-7} mmhg at 20°C (Bidleman et al. 1981) to 0.4 mmhg at 25°C (HSDB 1994) are reported in the literature. These disparities may be due to the different methods used to determine vapor pressure and/or to the varying compositions of the toxaphene mixtures used. Reliable vapor pressure estimates for well-characterized toxaphene mixtures are needed. Since toxaphene is a complex mixture, the toxicity of specific congeners in such original products as the pesticide technical-toxaphene will vary. Unfortunately, information on the toxicities of components in the original mixtures is limited to perhaps 10 congeners, the most familiar being the appreciably toxic and persistent toxicant A and toxicant B. Once in the environment, the toxic properties of congener metabolites are usually unknown (Bidleman et al. 1993). This situation seriously complicates efforts to quantify risks. Information on the physical and chemical properties of additional congeners would be helpful in prediction of environmental fate and transport processes for these mixtures.

Production, Import/Export, Use, Release, and Disposal. Information on the current production levels of toxaphene is not available. The most recent estimate of production levels was in 1982, the year that EPA restricted the use of toxaphene. Production levels that year were less than 2 million kg (EPA 1987a), substantially lower than in 1972 (21 million kg) when toxaphene was the most widely manufactured pesticide in the United States (Grayson 1981). It is estimated that current production levels continue to be low; however, information on production between 1982 and the present, as well as between 1972 and 1982, would be helpful in estimating potential human exposure to toxaphene.

Since all registered uses of toxaphene as a pesticide were cancelled in July 1990 in the United

States and all U.S. territories (EPA 1990b), readily available production estimates will obviously seem minuscule in the 1990s as compared to 10-20 years ago when toxaphene was the most widely used pesticide agent. In other parts of the world, however, toxaphene use continues at very high levels (Bidleman et al. 1989; Stem et al. 1993). These use levels outside western-bloc countries are almost impossible to estimate, but many researchers feel that these global levels are quite substantial (Lahaniatis et al. 1992; Stem et al. 1993). Since toxaphene, once volatilized, can be transported atmospherically over enormous distances, all terrestrial and aquatic ecosystems are still subject to low levels of exposure. Especially in terms of these atmospheric inputs, the best available monitoring information shows no demonstrable downward trends (Bidleman et al. 1992).

No current information on import and export quantities of toxaphene was identified. It is likely that toxaphene is currently not being imported into the United States as all registered uses of toxaphene as a pesticide were cancelled in July 1990 (EPA 1990b). Quantitative information on any import and export volumes is necessary to estimate potential human exposure to toxaphene.

In 1982, the use of toxaphene was restricted by EPA to its use as a pesticide on livestock, to control grasshopper and army worm infestation on cotton, corn, and small grains (in emergency situations only), and on banana and pineapple crops in Puerto Rico and the Virgin Islands (EPA 1982a). After July 1990, the pesticide registrations for all toxaphene formulations were cancelled in the United States and in all U.S. territories (EPA 1990b).

Because of its historic use as a pesticide, toxaphene has been widely distributed in the air, soil, surface water and sediments, aquatic organisms, and foodstuffs. Information on the current distributional patterns, which may involve localized hotspots, would be helpful in estimating human exposure.

Incineration in a pesticide incinerator is the preferred method of disposal for toxaphene (EPA 1974, 1980b, 1988c). Additional information on the amount of toxaphene disposed of by this method, as well as the amount of toxaphene disposed of or abandoned at hazardous waste sites, would be helpful for estimating the potential for human exposure.

According to the Emergency Planning and Community Right-to-know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1991, became available in May of 1993. Toxaphene is included under TRI because it is one of a very small number of pesticides indentified under the Clean Water Act as Priority Pollutants. The TRI database, however, contains no listings for toxaphene (TRI91 1993). While TRI does not constitute an exhaustive inventory, the absence of listings in TRI clearly indicates that there are currently no significant releases of toxaphene from production or processing facilities to any environmental media in the United States.

Environmental Fate. Information on the environmental fate of toxaphene congeners (as a chemical group) is only sufficient to permit a general understanding of the partitioning and widespread transport, of toxaphene mixtures in the environment. Limited data are available on transport and transformation of individual fractions of toxaphene mixture; however, composition of toxaphene mixtures varies among producers (Walter and Ballschmiter 1991; Worthing and Walker 1987). Additional information on the identity, physical/chemical properties, and environmental fate of toxic fractions of the mixture would be useful. However, the sampling and analytical methodology limitations that have contributed to the lack of availability of this type of data in the past have not been completely overcome. Therefore, the development of this information may be difficult. More information on the rates of biotransformation and abiotic reduction of toxaphene in soils and sediments under anaerobic conditions would improve the current understanding of toxaphene's environmental fate. The role of biotic transformations in aerobic environments following initaial reductive dechlorination needs to be clarified. In addition, the identity, toxicity, and environmental fate of the major transformation products need to be discerned. This information will be useful in making a more critical assessment of potential human exposure to the mixture.

Bioavailability from Environmental Media. Animal studies and case reports of human exposure indicate that toxaphene is absorbed following inhalation, oral, and dermal exposure (Kutz et al. 1991; Munn et al. 1985). Pharmacokinetics data indicate that toxaphene present in water or food is extensively absorbed; however, the degree to which toxaphene is absorbed as a result of inhalation of contaminated air or dermal contact with contaminated environmental media has not been well studied. The high K_{oc} for toxaphene indicates that it is adsorbed relatively strongly to soil, but it is not possible to estimate the extent to which toxaphene present on ingested soil would be absorbed from the gastrointestinal tract. The data available for plants indicate that the mixture is apparently not taken up appreciably by plants from contaminated soils and sediments. Toxaphene is not expected to be available to humans via ingestion of plants unless they have been recently treated with the mixture. Since all registered uses of toxaphene as a pesticide were cancelled in the United States and U.S. Territories in July 1990; ingestion of domestically grown agricultural commodities should no longer be a source for toxaphene. In addition, with the revocation of tolerances of toxaphene (September 1993) in all agricultural commodities; detection of any toxaphene residues will result in seizure of these products and removal from the marketplace (EPA 1993b). More information on the extent of absorption of components of the mixture following contact with contaminated air, water, or soil would be helpful in determining the potential health effects resulting from human exposure.

Food Chain Bioaccumulation. Laboratory bioassay and field monitoring data clearly indicate that toxaphene components are bioconcentrated by aquatic organisms. Available model ecosystem and field monitoring studies of aquatic food chains are sufficient to indicate that toxaphene bioaccumulates in aquatic organisms (Lowe et al. 1971; Sanborn et al. 1976; Schimmel et al. 1977; Swackhamer and Hites 1988). However, as the result of metabolism, toxaphene is not biomagnified to the same degree as other chlorinated compounds, such as DDT and PCBs (Evans et al. 1991; Ford and Hill 1991; Neithammer et al. 1984). While several studies show toxaphene is biomagnified in some ecosystems, several other studies show that little or no biomagnification of toxaphene occurs in other ecosystems because of effective metabolism of toxaphene by higher trophic level mammalian species (Anderson et al. 1988; Muir et al. 1988a, 1988b, 1992). Further information on the bioaccumulation and biomagnification potential of toxaphene in both terrestrial and aquatic food chains would be desirable to resolve differences observed in different ecosystems. These data will be helpful in assessing the potential for human exposure as a result of ingestion of contaminated food.

Exposure Levels in Environmental Media. Although a large amount of monitoring data is available for toxaphene, most of the data were collected 10 to 20 years ago when the mixture was widely used as a pesticide. Historic monitoring data exist for air (Kutz et al. 1976; EPA 1984b, 1986; Stanley et al. 1971), for surface water (Cole et al. 1984; Cooper et al. 1987; Staples et al. 1985), drinking water (Faust and Suffet 1966), and groundwater (Plumb 1987). Therefore, additional information on current levels in environmental media would be helpful in characterizing present day concentrations to which humans could be exposed. This is particularly important for concentrations of toxaphene in air, soils, and surface waters in the vicinity of hazardous waste sites. The data currently available are too limited to be useful in estimating the exposure of populations coming into contact with the mixture through inhalation of contaminated air, consumption of contaminated surface water, groundwater, or foodstuffs, and/or contact with contaminated soil. Reliable information is needed on current exposure levels in all environmental matrices and foodstuff (fish, shellfish, and terrestrial wildlife) in the vicinity of hazardous waste sites. Additional biomonitoring studies of both aquatic and terrestrial wildlife populations near hazardous waste sites, near waterbodies where fish consumption advisories are currently in force (RTI 1993), and in areas were toxaphene was historically used in agriculture applications (Ford and Hill 1991) are needed so that the information on levels of toxaphene in the environment can be used in combination with the known body burden of toxaphene to assess the potential risk of adverse health effects in populations living in these areas.

Exposure Levels in Humans. Exposure levels for the populations with either short-or long-term contact with hazardous waste sites are unknown. These levels currently cannot be estimated because of the lack of toxaphene concentration data for contaminated media in the vicinity of hazardous waste sites. Exposure of the general population has been estimated from levels in air and foodstuffs; however, the data upon which the estimates were based were obtained prior to the restrictions on toxaphene use. More current exposure data would be useful in assessing the exposure of the general populations via these routes. Pharmacokinetic data indicate that toxaphene rapidly redistributes to body fat and toxaphene has been identified in human breast milk fat from mothers (Vas and Blomkvist 1985). Tissue levels have not been obtained from persons exposed to toxaphene either as a result of contact with a hazardous waste site or though occupational exposure. This information would be useful in assessing the risk to human health for populations living in the vicinity of hazardous waste sites and occupational populations exposed through continued production of the mixture. This information is necessary for assessing the need to conduct health studies on these populations.

Exposure Registries. No exposure registries for toxaphene were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

5.7.2 Ongoing Studies

The U.S. Department of Agriculture has sponsored one study on toxaphene. Researchers at the University of California-Davis are currently conducting studies to identify major pesticide-degrading microorganisms, to isolate and identify their major degradation systems, and to develop necessary biotechnologies to use the biodegradative capabilities of these microorganisms for on-site degradation of pesticides. Toxaphene is one of several pesticides and organochlorine compounds currently being investigated.

Results of remedial investigations and feasibility studies conducted at the 58 NPL sites known to be contaminated with toxaphene will be added to sections of this profile on exposure levels in environmental media, exposure levels in humans, and exposure registries as they become available.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring toxaphene, its metabolites, and other biomarkers of exposure and effect to toxaphene. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

This chapter summarizes the methods available for the analysis of toxaphene in biological and environmental media. In designing a study and choosing a method, it is very important that adequate attention be paid to the extent of validation and field applicability. Some of the EPA methods have been validated, while some of the literature methods have not. It is the analyst's responsibility to determine the data quality needed before initiating the application of a particular method.

The analytical methods used to quantify toxaphene in biological and environmental samples are summarized below. Table 6-1 lists the applicable analytical methods for determining toxaphene in biological samples, and Table 6-2 lists the methods used for determining toxaphene in environmental samples.

6.1 BIOLOGICAL SAMPLES

The analysis and chemical characterization of toxaphene is difficult because of the extreme complexity of the compound. Commercial toxaphene is a complex mixture of chlorinated camphene derivatives containing more than 670 components (Jansson and Wideqvist 1983). Furthermore, widespread contamination from ubiquitous polychlorinated biphenyls (PCBs), 1,1-dichloro-2-2-bis (chlorphenyl)-ethane (DDE), and other organochlorine pesticides, which are also complex multi-isomeric chemicals, often interferes with toxaphene's analysis. Hence, identification of toxaphene in biological and environmental samples almost invariably involves rigorous sample preparation and clean-up procedures prior to chromatographic analysis (Gooch and Matsumura 1985; Matsumura et al. 1975; Nelson and Matsumura 1975). The determination of trace amounts of toxaphene in human tissues and fluids has been restricted to a limited number of analytical techniques. These include gas chromatography equipped with either an electron capture detector (GC/ECD), or a microcoulometric detector (GC/MC), or negative ion chemical ionization mass spectrometry (GC/NCI-MS), and thin-layer chromatography (TLC).

TABLE 6-1. Analytical Methods for Determining Toxaphene in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	R
Human tissues	Macerate tissue into a fine slurry; add anhydrous $Na_2 SO_4$ and acetone; warm, cool, and filter solution; add water and saturated $Na_2 SO_4$ solution to extract; extract with chloroform; add 5% KOH to chloroform extract; extract with water, dry ($Na_2 SO_4$) evaporate and dissolve residue in acetone	TLC	1 μ/ sample	94%	Te
Stomach washings	Filter sample and wash residue with water;add	TLC	1 μ/ sample	94%	Te

and urine	saturated solution of Na_2SO_4 and extract with hexane; filter extract through anhydrous Na_2SO_4 and evaporate to dryness; dissolve residue in acetone				
Human blood	Add 60% H_2SO_4 to blood sample; add hexane: acetone (9:1) to sample to solution and shake; centrifuge centrufuge and evaporate to dryness; dissolve residue in hexane	GC/ECD GC/MC	No data 10-40 ppb	100% 100%	Griff
Human blood	Add sample to a solution of dilute H_2SO_4 and 100% sodium tungstate, and swirl gently; filter solution and wash residue with water; dry with (Na_2SO_4) and extract with hexane; filter extract through anhydrous Na_2SO_4 and evaporate to dryness; dissolve residue in acetone	TLC	1 µ/ sample	94%	Te
Human breast fat	Homogenize sample; extract with petroleum other; centrifuge; dry	GC/ECD	No data	No data	Head a

	extract with anhydrous $Na_2 SO_4$;reduce the volume				
Fat	Shake sample with acetonitrile and centrifuge; remove acetonitrile extract; add pentane and concentrated $H_2 SO_4$ to remaining fat after acetonitrile extraction; shake and centrifuge; pool extracts; pass through activated alumina microcolumn	GC/ECD	No data	96-102%	Atuma
Fat	Extract sample with a mixture of hexane and diethyl ether; evaporate and dissolve extract in hexane; shake with $H_2 SO_4$ and analyze	GC/ECD	1.5 ngμL	61-98%	Wideqvist

GC/ECD = Gas chromatography/electron capture detector; GC/MC = Gas chromatography/microco

TABLE 6-1. Analytical Methods for Determining Toxaphene in Biological Samples

TABLE 6-2. Analytical Methods for Determining Tosaphene in Environmental Sample

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery
Air	Trap on chromasorb 102; extract with hexane	GC/ECD	0.234-0.926 ng/m^3	100% recovery

	extract with hexane		ng/m	recovery
Air	Collect air sample in an air sampling train equipped with prefilter and ethylene glycol; dilute ethylene glycol with water and extract with hexane; extract prefilter with hexane; pool extracts and dry (NA_2SO_4; concentrate extracts	GC/ECD	1-10 ng/m^3	No data
Ambient air	High volume sampler consisting of glass fiber filter with polyurethane foam (PUF) backup adsorbent. Flow rate approximately 200-280 L/min for 24 h. Extract filter and PUF in soxhlet with 5% ether in hexane. Clean-up using alumina column chromatography. Concentrate using K-D. (EPA Method TO4)	GC/ECD(EPA Method 608)	Generally >1 ng/m^3	No data
Drinking water	Extract sample with 15% dichloro-methane in hexane; dry with anhydrous Na_2SO_4; concentrate extract	GC/ECD or GC/MC or GC/electrolytic conductivity and GC/MS	0.001-0.01 µg/L(single component pesticide sample) 0.050-1.0 µg/L component	No data

			pesticide sample)	
Drinking water	Extract sample with dichloromethane, dry and solvent exchange to methyl-t-butyl ether (EPA Method 508)	GS/ECD (capillary column)	No data	No data
Drinking water, ground water, soil, sludges, wastes	Extract sample with organic solvent and clean up on Florisil column.	GC/ECD	0.24 µ/L (drinking water) to 24 mg/L (non-water miscible waste)	No data
Drinking water	Extract sample with auetone on a water sampling appaatus equipped with porous polyurethane plugs; elute extract through activated Florisil column with diethyl ether in petroleum ether	GC/ECD and GC/MS	0.01 ng/L recovery	100%
Waste water	Extraction with dichloromethane	Tandem MS	5 µ/sample	
Waste water	Extraction with dichloromethane, solvent exchange to hexane; Florisil clean-up	GC/ECD (packed column)	0.21 µg/L	96%
Waste water	Extract with 15% dichloromethane in hexane. Dry with sodium sulfate and concentrate with K-D. if needed, partition with	GC/ECD	No data	96%

	acetonitrile to remove fats and oils or fractionate using a Florisil column			
Municipal and industrial discharge water	Adjust to pH=11 and extract with dichloromethane. Concentrate using K-D after drying.	GC/MS	No data	No data
Municipal and industrial discharges	Extract with dichloromethane (no pH adjustment); solvent exchange to hexane during concentration; magnesia-silica gel clean-up; concentrate	GC/ECD	0.24 µg/L	80%
Municipal and industrial waste water, sludges	(1) if solids <1%, extract with dichloromethane. (2) For nonsludges with solids 1-30%, dilute to 1% and extract with methylene chloride. if solids >30% sonicate with methylene chloride/acetone. (3)For sludges: if solids <30% treat as in #2 above. if solids <30% sonicate with acetonitrile then methylene chloride. Back extract with 2% sodium sulfate. Dry with sodium sulfate, concentrate using K-D, purify using	GC with ECD,MC or electrolytic conductivity	910 ng/L (lower if many interferences)	76-122% at 5000 ng/ acceptable

	GPC, Florisil and/or SPE.			
Primary sludge	Extract sample with hexane: dichloromethane acetone (83:15:2); centrifuge and concentrate extract; load on Florisil column and elute with 20% acetone in hexane	GC/ECD and GC/MC	No data	85-93%
Soil	Add water and extract with methanol: toluene (1:1); load extract onto chromaflex column containing Florisil; concentrate sample; add 43% methanolic KOH solution and reflux; extract with hexane; load extract on Florisil column and elute with 6% diethyl ether in hexane	GC/MS and HPLC	0.05 µg/g	76-91% recovery
Soil	Soxhlet extraction using methylene chloride or sonication with methylene chloride: acetone (1:1, v/v). GPC or SPE clean-up	GC/electron-capture negative ion mass spectrometry	100 µg/kg	No data
Sediment, and mussel tissue	Extract sample with hexane; elute from alumina column, concentrate eluent	HPLS followed by GC/FID or GC/ECD	<1 ng/g	95-100% recovery
Pesticide formulation	Extract sample 50% methanolic KOH; elute with ether from	GC/ECD	1 ng/ sample	No data

	Florisil			
Pesticide formulation	Remove solvent (xylene) from pesticide sample by reduced pressure; extract with hexane	Open tubular GC column and GC/TLC	No data	No data
Pesticide formulation	Extract sample in hexane	TLC	1 µg/sample	No data
Pesticide formulation	Dissolve sample in hexane; load on alumina column; elute with hexane, then 20% methylene chloride in benzene and finally 100% methanol;	GC/ECD or GC/FID	No data	No data
Cotton leaves	Extract sample with water and petroleum ether; add methanolic KOH and heat; concentrate extract	TLC followed by GC/ECD	0.16-0.45 µg/ cm^2	No data
Various produce	50 g homogenized sample extracted with acetonitrile, filtered, and salt added to affect phase separation. Evaporate to near dryness and reconstitute in benzene	GC/ECD	2 ppm	No data
Fruits and vegetables	Extract with acetone in blender; filter and extract with petroleum ether/dichloromethane; evaporate extract; dissolve residue in	GC/ECD	No data	No data

	minimum amount of acetone			
Cucumber	Blend sample with acetone; suction filter suction dichloromethane (1.1); dry (Na_2SO_4) organic extract and shake with saturated NaCI solution; concentrate sample extract; load sample on Florisil column and elute with 15% ethyl ether in petroleum ether; concentrate to small volume and analyze	GC/ECD or FID	4.34 ppm	113% recovery
Fortified extracts (various foods)	Prepare sample solution With acetone or hexane; add diphenylamine and zinc chloride solution; evaporate to dryness; heat residue (250°C) for a few minutes; dissolve residue complex in acetone; and analyze at 640 nm	Spectrophotometer	<1 ppm	69-100% rec
Molasses	Dilute sample with water; extract with hexane: isopropanol	GC/ECD	0.03 mg/kg	No data
Meat	Blend with ethyl acetate; dry (Na_2SO_4-) homogenate and filter; treat extract	GC/ECD	No data	76-79% recovery

	with KOH and warm; cool and extract with hexane; elute from Florisil column			
Bovine Defibrinated Whole blood	Dilute blood with water and shake on a vortex mixer; add hexane and centrifuge at 1,800 rpm;inject hexane phase into GC	GC/ECD	0.58 µg/mL	73.4% recovery
	Add sample to 88% formic acid and shake on a vortex mixer; add hexane and mix thoroughly; centrifuge at 1,800 rpm; shake organic extract with 5% potassium carbonate; concentrate extract	GC/ECD	0.465 µg/mL	71.7% recovery
	Add sample to 88% formic acid and shake; load onto Florisil column and elute with 6% diethyl ether in petroleum ether; concentrate and wash with hexane	GC/ECD	0.026 µg/mL	103.4% recovery
Lard	Extract with peytoleum ether;centrifuge;dry extract with anhydrous NA_2SO_4	GC/ECD	1.37 µg/G	46.5-107.3% recovery
Poultry fat	Place sample in a glass funnel with glass wool plug; place funnel in a beaker and heat until	GC/ECD	0.475-0.908 ppm	92.6-96.9% recovery

	fat ceases to drip; mix thoroughly			
Milk fat	Centrifuge and pass fat sample through Florisil column	GC/ECD and GC/MS	<10 ppb (ECD) 7ppb(MS)	No data
Milk,fat,blood and alfalfa hay	Add sample to an aqueous solution of KOH and EtOH; extract with benzene	GC/ECD 0.1 to 0.5 ppm	74.1-95.2% recovery	No data
Milk and butter	Add sample to KOH;shake and heat;cool sample and extract with hexane; centrifuge and elute extract over Florisill column	GC/ECD	No data	78-88% recovery
Human breast milk	Centrifuge milk sample; freeze-dry fat concentrate; dissolve in acetone and cool to -60 °:C; dissolve residue in hexane and shake with concentrated H_2SO_4 clean sample on silica gel column	GC/ECD and GC/NCI-MS	100 ng/g	No data
Fish (whole)	Freeze; grind in blender with dry ice; mix with anhydrous NA_2SO_4; extract in a column with hexane: acetone (1:1), followed by methanol	NCI-MS	75 pg/sample	98% recover
Fish tissues	Extract Tissues with a mixture of hexane and acetone followed by a	GC/NCI-MS	No data	No data

	second extraction with hexane and diethyl ether; evaporate and dissolve lipid extract in hexane; shake with H_2SO_4 to remove lipid			
Fish tissue	Homogenize 10 g sample with hexane:acetone (1:2.5) under acid condition, extract twice more with 10% diethyl ether in hexane. Treat with 98% H_2SO_4 and clean up using GPC and silica gel chromatography.	GC/NCI-MS	No data	94% (RSD=11%) at 19ng/g
Fish tissue	Pulverize tissue with anhydrous sodium sulfate and extract with acetone. Transfer to hexane and concentrate. Clean up using dry-packed Florisil, wet-packed Florisil and silica gel.	GC/MS (Selected ion Monitoring)	0.1 ng/g	90%(% RSD=7%)at 100 ng

GC/ECD = Gas chromatograph/electron capture detector; GC/FID = Gas chromatography/flame i
spectroscopy; GC/MC = Gas chromatography/microcoulometry; GC/MS = Gas chromatography/mass
ionization mass
spectrometry; GPC = Gel permeation chromatography; HPLC = High performance liquid chromat
TLC = Thin-layer
chromatography

TABLE 6-2. Analytical Methods for Determining Tosaphene in Environmental Samples

The most prevalent analytical technique employed to determine trace amounts of toxaphene in biological and environmental samples is GC/ECD because ECD offers a uniquely high sensitivity for substituents such as halogens. Griffith and Blanke (1974) and Head and Burse

(1987) employed GC/ECD for analysis of toxaphene in human blood and breast milk fat, respectively. Identification of low ppb levels of toxaphene in human blood was achieved by GC/MC (Griffith and Blanke 1974). The advantages of GC/MC are that the system is linear, more specific, and a lower temperature is generally required to vaporize the compound in the GC column. A GC method that uses electron capture NCI-MS for detection has been developed by Vaz and Blomkvist (1985) to quantitatively and selectively detect components of toxaphene at ppb (ng/g) levels in human breast milk. Vaz and Blomkvist (1985) demonstrated that several mass (M) fragments containing mainly (M-35) ions can be identified, thereby giving relatively simple mass spectra. More important, however, fragmented ions from contamination by other organochlorine compounds were not detected because they gave weak NCI- MS spectra. Jansson et al. (1991) have also used GC/NCI-MS to detect toxaphene residues in fish at the ppb level.

In addition to direct measurement of toxaphene in biological media, it is also possible to determine the level of metabolites in biological tissues and fluids. Tewari and Sharma (1977) developed a TLC method for determination of toxaphene and its metabolites (dechlorinated and dehydrochlorinated toxaphene) in urine, stomach washings, and blood. A detection limit of 1x10 g of toxaphene per sample was achieved. The authors employed a series of solvent systems and chromogenic reagents on silica gel plates impregnated with silver reagents and copper sulfate for separation of the pesticides. The TLC technique is, however, laborious and time consuming. Becker et al. (1989) used GC/ECD and GC/NCI-MS for the determination of dechlorinated toxaphene residues.

Despite the availability of advanced instrumental methods, the accurate quantitative determination of the level of toxaphene is difficult because of inherent differences between the GC fingerprint pattern of the technical toxaphene standard and the pattern found in human fluid extracts containing toxaphene. These differences reflect changes caused by metabolism and degradation of the original compound.

6.2 ENVIRONMENTAL SAMPLES

Residues of toxaphene are detectable in the environment because of its use as a piscicide and its use as a pesticide on field crops, fruits, vegetables, and uncultivated lands. The identification and quantification of toxaphene in environmental samples is complicated by changes in the numbers and relative sizes of constituent peaks (components) due to the difference in their rates of degradation, sorption, and volatilization in the environment.

GE/ECD, sometimes in combination with GC/MS, is the most frequently used analytical method for characterization and quantification of toxaphene in air, drinking water, fish, and other environmental samples (Boshoff and Pretorius 1979; Cairns et al. 1981; EPA 1976c; EPA 1985c; Kutz et al. 1976; Luke et al. 1975; Thomas and Nishioka 1985; WHO 1984; Wideqvist et al. 1984). Analysis of the sample includes extraction in organic solvent; a Florisil silica, gel permeation, or thin-layer chromatography clean-up step; and detection by gas chromatography (Atuma et al. 1986; Ault and Spurgeon 1984; EPA 1976b; Head and Burse 1987; Ismail and Bonner 1974; Maiorino et al. 1980; Saleh and Casida 1977; Seiber et al. 1975). A typical gas chromatogram contains a series of hills and valleys with three main peaks (EPA 1982b; Gomes 1977). Detection limits of toxaphene residues in fish and drinking water were 50 ng of toxaphene per gram of sample and 1 ng of toxaphene per gram of sample, respectively (EPA 1987a; EPA 1976c). GCsol;ECD is the standardized method used by EPA (method 8080) for determining toxaphene in water samples. A detection limit of 0.24 µg toxaphene per liter of sample was achieved (EPA 1986g).

Archer and Crosby (1966) developed a confirmatory method for toxaphene analysis in environmental samples that involved dehydrohalogenating (in 50% methanolic potassium hydroxide) the residue extract prior to GC analysis. The gas chromatogram indicated one main peak and several minor peaks. Also, the detector response was doubled, thereby increasing the sensitivity of this procedure. While this method was also rapid, its main application was in samples where toxaphene was the major residue. In samples with multiple organochlorine pesticide residues, it would be difficult to measure accurately all the residues and quantify the amount of toxaphene (Archer and Crosby 1966; Bigley et al. 1981; Crist et al. 1980; Gomes 1977). Recoveries from various samples are generally good with detection limits at levels of less than 1 ppm.

The tandem MS method has been used as an alternative to GC/MS.This method employs the technique of collision-activated dissociation on a triple quadruple mass spectrometer. This facilitates direct and rapid qualitative and semiquantitative analysis of toxaphene samples in both liquid and solid environmental matrices at the 10-100 ppb level (Hunt et al. 1985). Additional features of the tandem MS include the elimination of most wet chemical and chromatographic separation steps, detection of both known and unknown compounds by molecular weight and functional group, and a total analysis time per sample of less than 30 minutes. A disadvantage is that tandem MS is somewhat less specific than GC/MS in the identification of some isomeric compounds.

Techniques developed by Jansson and Wideqvist (1983) and modified by Swackhamer et al. (1987) indicated that toxaphene can be detected at 75 pg per sample (approximately 1.2 ng/g) in fish using methane NCI-MS. The authors noted that the NCI-MS technique is more specific and 100 times more sensitive than electron impact (EI) or chemical ionization (CI) mass spectrometry and GC/ECD. In combination with aselected ion monitoring program, specific fragment ions can be monitored without any pre-separation column chromatography to eliminate other organochlorine pesticides that coelute with toxaphene (Swackhamer et al. 1987). Furthermore, NCI-MS spectra are less complex than EI or CI-MS spectra and contain higher mass ions due to successive losses of chloride and hydrochloride from the molecular ion. Jansson et al. (1991) reported a GC/NCI-MS method for toxaphene in fish that allowed detection of levels below 19 ng/g.

Shafer et al. (1981) reported that the combined data of a gas chromatograph coupled to a fourier-transform infrared spectrometer (GC/FT-IR) and GC/MS provide complementary information that leads to a better understanding and identification of the EPA's priority pollutants (including toxaphene) in air. Both GC/FT-IR and GC/MS separations were performed quickly and efficiently on wall-coated open tubular capillary columns.

A semi-specific spectrophotometric method for toxaphene analysis in fortified extracts of various foods was developed by Graupner and Dunn (1960). It was based on measuring the absorbance at 640 nm of a greenish-blue diphenylamine-toxaphene complex that was formed by reacting a sample extract with diphenylamine in the presence of zinc chloride. Several other organochlorine pesticides also reacted under these conditions, but only a few formed complexes that absorbed appreciably at 640 nm, thereby causing some interference with toxaphene analysis. A detection limit of less than 1 ppm of toxaphene was reported (Grauper and Dunn 1960).

Recently, Petrick et al. (1988) employed high-performance liquid chromatography (HPLC) as a clean-up technique prior to GC analysis. Petrick and co-workers efficiently separated toxaphene residues from other organochlorinated compounds in fat-rich samples with quantitative recovery. A detection limit of less than 1 ng of toxaphene per gram of sample was achieved by GC/ECD. The authors noted that the HPLC technique is highly efficient and reproducible and has a low consumption of solvents and high sample loading capacity.

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of toxaphene is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of toxaphene.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs.

Methods for Determining Biomarkers of Exposure and Effect. Methods are available for detecting and quantifying levels of toxaphene in the blood and milk fat of humans. The precision, accuracy, reliability and specificity of these methods have been reported. These methods are sufficiently sensitive to determine background levels of toxaphene in the general population and levels at which adverse health effects would begin to occur. Pharmacokinetic data indicate that toxaphene rapidly redistributes to fat; therefore, blood levels would be useful for identifying very recent exposures to toxaphene. Levels in milk fat are retained somewhat longer, but these levels decrease within weeks of cessation of exposure.

A highly sensitive and specific NCI-MS technique has been employed to detect components of toxaphene at ppb levels in breast milk without the interference of other organochlorine pesticides (Vaz and Blomkvist 1985). GC/ECD and GC/MS can also detect trace amounts of toxaphene in human tissues and fluids following an efficient sample preparation and rigorous clean-up procedures. Currently, the only method available for analysis of toxaphene metabolites is TLC (Tewari and Sharma 1977). There is a growing need for research and development of highly sensitive and quantitative methods for determination of toxaphene metabolites. These methods would be useful, since they would allow investigators to assess the risks and health effects of long-term low-level exposure to toxaphene.

Currently, no methods are available to quantitatively correlate monitored levels of toxaphene in tissues or fluids with exposure levels or toxic effects in humans. If methods were available, they would provide valuable information on systemic effects following exposure to trace levels of toxaphene.

No specific biomarkers of effect have been clearly associated with toxaphene poisoning. Some biological parameters have been tentatively linked with toxaphene exposure, but insufficient data exist to adequately assess the analytical methods associated with measurement of these potential biomarkers.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Human exposure to toxaphene occurs primarily by inhalation of ambient air, ingestion of contaminated foodstuffs and through contact with contaminated soil and surface water. Reliable analytical methods are available to detect background levels of toxaphene in a wide range of environmental matrices. Toxaphene levels of 75 pg/sample (approximately 1.2 ng/g) can be detected in fish using the NCI-MS technique (Swakhamer et al. 1987). However, there is a need to implement more refined software to process efficiently the data generated by the NCI-MS technique. GC/ECD is the standardized analytical method used by EPA (1986g, method 8080) to determine toxaphene in water samples at sub ppb levels. GC/ECD, GC/MS, and tandem MS can detect and quantify toxaphene in air, soil, plant material, fish, water, milk, fat, and meat at ppb levels. No additional analytical methods for detecting low levels of toxaphene are needed.

Little is known about the toxic properties of toxaphene congener metabolites in the environment (Bidleman et al. 1993). Additional analytical methods specifically targeted at toxaphene metabolites and degradation products are needed to support such investigations.

6.3.2 Ongoing Studies

No ongoing studies concerning techniques for measuring and determining toxaphene in biological and environmental samples were reported.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding toxaphene in air, water, and other media are summarized in Table 7-1. ATSDR has derived an acute-duration oral MRL of 0.005 mg/kg/day for toxaphene based on a hepatotoxicity study (Mehendale 1978) and an intermediate-duration oral MRL of 0.001 mg/kg/day based on behavioral effects (Chu et al. 1986). No EPA reference concentration or reference dose exists for the compound.

Toxaphene is on the list of chemicals appearing in The Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA) (EPA 1988a). Section 313 of Title III of EPCRA requires owners and operators of certain facilities that manufacture, import, process, or otherwise use the chemicals on this list to report annually their release of those chemicals to any environmental media.

OSHA requires employers of workers who are occupationally exposed to toxaphene to institute engineering controls and work practices to reduce employee exposure to, and maintain employee exposure at, levels at or below permissible exposure limits (PEL). The employer must use engineering and work practice controls, if feasible, to reduce exposure to or below an 8-hour time-weighted level (TWA) of 0.5 mg/m^3. Respirators must be provided and used during the time period necessary to install or implement feasible engineering and work practice controls (OSHA 1989).

Also, to prevent or reduce skin absorption, an employee's skin exposure to toxaphene must be prevented or reduced to the extent necessary in the circumstances through the use of gloves, coveralls, goggles, or other appropriate personal protective equipment, engineering controls, or work practices.

Toxaphene is regulated by the Clean Water Effluent Guidelines as stated in Title 40, Sections 400-475, of the Code of Federal Regulations. For each point source category, toxaphene may be regulated as one of a group of chemicals controlled as Total Toxic Organics, or may have a specific Regulatory Limitation, or may have a Zero Discharge Limitation. The one point source category for which toxaphene is controlled as a Total Toxic Organic is electroplating (EPA 1981b). The point source category for which toxaphene has a Zero Discharge Limitation is steam electric power generation (EPA 1982d).

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), food tolerance restrictions for toxaphene range from 0.1 to 7 ppm (EPA 1971, 1986d).

The Resource Conservation and Recovery Act (RCRA) identifies toxaphene as a hazardous waste in three ways: (1) when it exceeds a toxicity characteristic leaching procedure test concentration of 0.5mg/L (EPA 1990b); (2) when it occurs as a waste from specific sources (EPA 1981c); and (3) when discarded as a commercial product, off-spec species, container residue, or spill residue (EPA 1980b). Toxaphene is also designated a hazardous air pollutant under the Clean Air Act Amendments of 1990.

7-1. Regulations and Guidelines Applicable to Toxaphene

Agency	Description	information	Reference

INTERNATIONAL			
WHO		NA	
IARC	Group(cancer ranking)	2B[a]	IARC 1987
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL (TWA)	0.5 mg/m^3	54 FR 2928 (1/19/89) 29 CFR 1910.10 OSHA 1989
	PEL (Ceiling)	skin designation	54 FR 2928 (1/19/89) 29 CFR 1910.10 OSHA 1989
EPA OAR	Hazardous Air Pollutant	none	Clean Air Act Amendments Title III, Section 112 (b
b. Water	Effluent Guidelines and Standards: Toxic pollutants	none	40 CFR 401.15 EPA 1986b
	Pretreatment Regulations: Appendix B -- 65 Toxic Pollutants	none	40 CFR 403 EPA 1986b
	Effluent Guidelines and Standards: Electroplating Definition of Total Toxic Organic	>0.01 mg/L	40 CFR 413.02 EPA 1981b
	Effluent Guidelines and Standards: Steam Electric Power Generation: Appendix A - 126 Priority Pollutants	none	40 CFR 413.02 EPA 1982d

Effluent Guidelines and Standards: Metal Finishing - Definition of Total Toxic Organic	>0.01 mg/L	40 CFR 433.11 EPA 1983a
Applicability; Description of the Organic Pesticide Chemicals Manufacturing Subcategory	none	40 CFR 455.20 EPA 1978b
Designation of Hazardous Substances: Section 311 of the Clean Water Act	1 lb	40 CFR 117.3 EPA 1979d
Appendix D -- NPDES Permit Application Testing Requirements (122.21)	none	40 CFR 122 EPA 1983b
Form 2D	none	40 CFR 122 EPA 1983b
Instructions -- Form 2C	NA	40 CFR 125 EPA 1979b
Toxic Pollutant Effluent Standards	none	40 CFR 129.4 EPA 1977b
Toxaphene Effluent Standard	0 - 1.5μ/L discharge/day	40 CFR 129.103 EPA 1977b
Identification of Test Procedures	none	40 CFR 136.3 EPA 1973
Method 608 -- Organochlorine Pesticides and PCBs	none	40 CFR 136 EPA 1973
Method 625 -- Base/Neutrals and Acids	none	40 CFR 136 EPA 1973

	Organic Chemicals Other Than Total Trihalomethanes, sampling and Analytical Requirements	0.01 mg/L (detection limit)	40 CFR 141.24 EPA 1975
	Public Notification	none	40 CFR 141.32 EPA 1975
ODW	Maximum Contaminant Level Goals for Organic Contaminants	0 mg/L	40 CFR 141.50 EPA 1975
	Maximum Contaminant Level for Organic Contaminants	0.003 mg/L	40 CFR 141.61 EPA 1975
	Appendix 1 to 40 CFR Part 257 -- Maximum Contaminant Levels (MCLs)	0.005 mg/L	40 CFR 257 EPA 1979c
c. Food			
EPA	Tolerance range for agriculture products	0.1-7 ppm	40 CFR 180.138 EPA 1971
		0.05-1ppm (Interim tolerances)	40 CFR 180.319 EPA 1971
d. Other EPA OERR/ CEPP	Reportable Quantity	1 lb.	54 FR 33418 (8/14/89) 40 CFR 302 EPA 1985a
	Designation of hazardous substances	none	40 CFR 302.4 EPA 1985a
	Chemicals and chemical categories to which this part applies (Toxic Release Inventory)	25,000 lbs. mfd. or processed 10,000 lbs. otherwise used	40 CFR 372.65 EPA 1988a
EPA OSW	Municipal Solid Waste Landfills: Design Criteria - MCL for Upper	0.005 mg/L	40 CFR 258.40 EPA 1991

Aquifer		
Municipal Solid Waste Landfills: Appendix II	2µ/L (Practical Quantitation Limit)	40 CFR 258.40 EPA 1991
Toxicity characteristic	0.5 mg/L	40 CFR 261.24 EPA 1980b
Hazardous wastes from specific sources	none	40 CFR 261.32 EPA 1980b
Discarded commercial chemical products, off-specification species, container residues, and spill residues thereof	none	40 CFR 261.33 EPA 1980b
Appendix VII - Bsis for Listing Hazardous Waste	none	40 CFR 261 EPA 1980b
Appendix VIII - Hazardous Constituents	none	40 CFR 261 EPA 1980b
Appendix IX - Wastes Excluded Under 260.20 and 260.22	none	40 CFR 261 EPA 1980b
Groundwater concentration limits	0.005mg/L	40 CFR 264.94 EPA 1980c
Appendix IX - Groundwater Monitoring List	2 µg/L limit)	40 CFR 264 EPA 1980c
Appendix III - EPA interim Primary Drinking Water standards	0.005 mg/L	40 CFR 265 EPA 1980d
Appendix VII - Health-based Limits for exclusion of Waste-Derived Residues	$5x10^{-3}$mg/kg	40 CRC 266 EPA 1985b
Identification of Wastes to	none	40 CFR 268.11

	be Evaluated by August 8, 1988		EPA 1986c
	Identification of Wastes to be Evaluated by june 8, 1989	none	40 CFR 266 EPA 1988c
	Treatment Standards Expressed as Specified Technologies	none	40 CFR 266.42 EPA 1986c
	Treatment Standards Expressed as Waste Concentration	none	40 CFE 268.43 EPA 1988c
	Appendix III-List of Halogenated Organic Compounds Regulated Under 268.32	none	40 CFR 268 EPA 1987c
EPA-OPTS	Tolerances for Related Pesticide Chemcials	none	
	Toxaphene; Tolerances for Residues	0.1-7 ppm	40 CFR 180.138 EPA 1971
	interim Tolerances	0.5 - 1ppm	40 CFR 180.319 EPA 1971
	Food Additives Permitted in Food for Human Consumption: Toxaphene in Soybean oil	6 ppm	40 CFR 185.575 EPA 1982c
CPSC	Consumer Product Limits	NA	
ACGIH	Ceiling Limit Occupational Exposure (TLV-TWA)	0.5 mg/m^3 (skin)	ACGIH 1986
	TLV-STEL	1 mg/m^3	ACGIH 1986
NOSH	Recommended Exposure Limit	lowest feasible	NIOSH 1992

NOSH	Recommended Exposure Limit for Occupational	lowest feasible	NIOSH 1992
	Exposure (TWA)	concentration (skin)	
	Recommended Exposure Limit for occupational	lowest feasible	NIOSH 1992
	Exposure (ceiling)	concentration (skin)	
	immediately Dangerous to life and Health	200 mg/m^3	EPA 1987d
EPA	q_1^* Cancer Slope Factor (inhalation exposure)	$3.2x10^{-4}mg/$	IRIS 1
	10-d Health Advisory (Child & adult)	0.04 mg/>L	EPA 1992a
	maximum Contaminant Lavel	0.003 mg/L	40 CFR 141.50 56 FR 3526 (1/30/91)
	Maximum Contaminant Level Gold	0.0 mg/L	40 CFR 141.161 56 FR 3526 (1/30/91)
	q_1^* Cancer Slope Factor (oral exposure	1.1x10° mg/ kg L	IRIS 1994
EPA	Cancer Classification	B2&bata	IRIS 1994
	Hazard Ranking	NA	
NTP	Cancer classification	NA	
NIOSH	Cancer Classification	Potential occupational	NIOSH 1992

		carcinnogen	
	consumer products Limit	NA	
a. Air:			
	Acceptabile ambient air concentration guidelines or standards		NATICH 1992
AZ	1 hr. avg. time	3.7 μ/m^3	
	24 hr. avg. time	1.5 μ/m^3	
	Annual avg. time	4.0x10^{-3} μg/m^3	
CT	8 hr. avg. time	2.5 μg/m^3	
FL-FTLDLE	8 hr. avg. time	5.0x10^{-3} μg/m^3	
FL-PINELLA	8 hr. avg. time	5.0 μg/m^3	
	24 hr. avg. time	1.2 μg/m^3	
	Annual avg. time	3.1x10^{-3} μg/m^3	
FL-TAMPA	8 hr. avg. time	5.0x10^{-3} μ/m^3	
KS-KC	Annual avg. time	3.13x10^{-3} μ/m^3	
MI	Annual avg. time	3.0x10^{-3} μ/m^3	
ND	8 hr. avg. time	5.0x10^{-3} μ/m^3	
	1 hr. avg. time	1.0x10^{-2} μ/m^3	
	Avg. time NA	0.0 BACT	
NV	8 hr. avg. time	1.2x10^{-2} & mu;/m^3	
NY	1 yr. avg. time	1.67 μ/m^3	

OK	24 hr. avg. time	5.0 μ/m^3	
PA-PHIL.	1 yr. avr. time	1.2 μ/m^3	
	Annual avg. time	1.2 μ^3	
SC	24 hrs. avg. time	2.5 $\mu g/m^3$	
TX	30-min. avg. time	$5.0x10^{-1}$ $\mu g/m^3$	
	Annual avg. time	5.0 $\mu g/m^3$	
VA	24 hr. avg. time	8.3 $\mu g/m^3$	
WA-SWEST	Annual avg. time	$3.0x10^{-3}$ $\mu g/m^3$	
	24-hr. avg. time	1.7 $\mu g/m^3$	
b. Water			
	Water Quality:Human Health		CELDs 1993
AL	Drinking water standard	5.0 µg/L	FSTRAC 1990
AZ	Domestic water source	3.0 µg/L	CELDs 1993
	Fish consumption	0.0008 µg/L	CELDs 1993
	Drinking water guideline	0.03 µg/L	FSTRAC 1990
	Drinking water standard	5.0 µg/L	FSTRAC 1990
CA		0.21 µg/L	CELDs 1993
CT	Organisms only	0.00075	CELDs 1993
	Organisms and water only	0.00073	CELDs 1993
DE	Freshwater fish ingestion	0.93 ng/L	CELDs 1993
	Freshwater fish & water ingestion	0.91 ng/L	CELDs 1993
	Marine/estuarine fish/shellfish ingestion	0.13 ng/L	CELDs 1993
HI	Fish consumption	0.00024 µg/L	CELDs 1993
ID	All Classes - Upper value	0.005 mg/L	EPA 1988b
IL	Public and food processing water supply standard	0.005 mg/L	EPA 1988b
IN		0.9973 µg/L	CELDs 1993
KY	Consumption of fish tissue	0.00073 µg/L	CELDs 1993

	Domestic water supply	0.00071 μg/L	CELDs 1993
LA	Drinking water supply	0.24 ng/L	CELDs 1993
	Non-drinking water supply	0.24 ng/L	CELDs 1993
MA	Drinking water standard	5 μg/L	FSTRAC 1990
ME	Drinking water guideline	0.3 μg/L	FSTRAC 1990
MD	Drinking water	5 μg/L	CELDs 1993
	Fish consumption	0.0073 μg/L	CELDs 1993
MN	Drinking water standard	5 μg/L	FSTRAC 1990
	Drinking water guideline	0.3 μg/L	FSTRAC 1990
MO	Fish consumption	0.000073μg/L	CELDs 1993
	Drinking water	0.000071 μg/L	CELDs 1993
MS	Organisms only	0.00075 μg/L	CELDs 1993
	Water & organisms	0.00073 μg/L	CELDs 1993
NJ	Class FW2	0.013 μg/L	CELDs 1993
	All SE, SC classes	0.005 μg/L	CELDs 1993
	Toxic effluent limitations for	0.71 ng/L	CELDs 1993
	potable water	0.71 ng/L	CELDs 1993
NV	Municipal or domestic	0.005 mg/L	CELDs 1993
	Industrial	0.005 mg/L	CELDs 1993
NY	Class GA	Not detectable	CELDs 1993
	Class A, A-S, AA, AA-S, B.C, SA, SB, SC	0.005 μg/L	CELDs 1993
	Class D	1.0 μg/L	CELDs 1993
OH	Public water supply	0.00071 μg/L	EPA 1988b
OK	Public and private water supply	0.005 mg/L	EPA 1988b
OR	Water and fish ingestion	0.71 ng/L	CELDs 1993
	Fish consumption only	0.73 ng/L	CELDs 1993
	Drinking water MCL	0.005 mg/L	CELDs 1993
RI	Drinking water standard	5 μg/L	FSTRAC 1990
	Drinking water guideline	0.03 μg/L	FSTRAC 1990
	Class A: upper value	1.6 μg/L	EPA 1988b
	ClassA: secondary upper limit	0.013 μg/L	EPA 1988b
SD	Domestic water	0.00071 μg/L	CELDs 1993
	All other sources	0.00073 μg/L	CELDs 1993
TN		5 μg/L	CELDs 1993
UT	Domestic source; maximum; Class 1C	5 μg/L	CELDs 1993
VA	Surface public water supply	0.005 mg/L	EPA 1988b
VT	Class A or B waters	0.71 ng/L	CELDs 1993

	Class C waters	0.73 ng/L	CELDs 1993
	Drinking water standard	0.031 µg/L	FSTRAC 1990
WI	Sport fish community-public water supplies	5.6 ng/L	CELDs 1993
	Cold water communities - public water supply	1.7 ng/L	CELDs 1993
	Great Lakes communities - public water supply	1.7 ng/L	CELDs 1993
	Warm water sport fish communities-non-public water supplies	5.7 ng/L	CELDs 1993
	Cold water communities-non water supplies	1.7 ng/L	CELDs 1993
	Warm water forage and limited forage fish communities and limited aquatic life - non-public water supplies	62,000 µg/L	CELDs 1993
WV	Criteria based on body burden of µg/L; all water uses	0.71 ng/L	CELDs 1993
	All Classes - upper value	0.005 µg/L	EPA 1988b
Water Quality: Aquatic Life			
AL	Acute- freshwater	0.73 µg/L	CELDs 1993
	Chronic-freshwater	0.0002 µg/L	CELDs 1993
	Acute-Marine	0.21 µg/L	CELDs 1993
	Chronic-marine	0.0002	CELDs 1993
AR	Chronic	0.002 µg/L	CELDs 1993
	Acute	0.73 µg/L	CELDs 1993
	All Classes: upper value	2.4 µg/L	EPA 1988b
	All Classes: secondary upper limit	0.013 µg/L	EPA 1988b
AZ	Acute-cold water fishery	0.73	CELDs 1993
	Acute-warm water fishery	0.73	CELDs 1993
	Acute-effluent dominated water	0.73	CELDs 1993
	Acute-ephemeral	1100	CELDs 1993
	Chronic-cold water fishery	0.0002	CELDs 1993
	Chronic-warm water fishery	0.02	CELDs 1993
	Chronic-effluent dominated water	0.02	CELDs 1993
	Chronic-ephemeral	1.5	CELDs 1993

CT	Acute-freshwater	0.73	CELDs 1993
	Chronic-freshwater	0.002	CELDs 1993
	Acute-salt water	0.21	CELDs 1993
	Chronic-salt water	0.0002	CELDs 1993
DE	Acute-freshwater	0.78 µg/L	CELDs 1993
	Chronic-freshwater	0.0002 µg/L	CELDs 1993
	Acute-marine	0.21 µg/L	CELDs 1993
	Chronic-marine	0.0002 µg/L	CELDs 1993
HI	Acute-freshwater	0.73 µg/L	CELDs 1993
	Chronic-freshwater	0.0002 µg/L	CELDs 1993
	Acute-saltwater	0.21 µg/L	CELDs 1993
	Chronic-saltwater	0.0002 µg/L	CELDs 1993
IN	Acute	0.0002 µg/L	CELDs 1993
	Chronic	0.73 µg/L	CELDs 1993
	Special aquatic life waters: upper value	0.013 µg/L	EPA 1988b
KY	Chronic	0.0002 µg/L	CELDs 1993
	Acute	0.73 µg/L	
LA	Acute-freshwater	0.73 µg/L	CELDs 1993
	Acute-marine water	0.21 µg/L	CELDs 1993
	Chronic-freshwater	0.0002 µg/L	CELDs 1993
	Chronic-marine water	0.0002 µg/L	CELDs 1993

MD	Acute-freshwater	0.73 µg/L	CELDs 1993
	Chronic-freshwater	0.0002 µg/L	CELDs 1993
	Acute-salt water	0.21 µg/L	CELDs 1993
	Chronic-salt water	0.0002 µg/L	CELDs 1993
	All Classes - upper value	0.005 µg/L	EPA 1988b
MS	Acute-freshwater	0.73 µg/L	CELDs 1993
	Chronic-freshwater	0.0002 µg/L	CELDs 1993
	Acute-salt water	0.21 µg/L	CELDs 1993
NE	All classes - upper value	0.005 mg/L	EPA 1988b
NC	Freshwater	0.0002 µg/L	
	Tidal saltwater - upper value	0.07 µg/L	EPA 1988b
ND	Chronic	0.002 µg/L	CELDs 1993
	Acute	0.73 µ:g/L	CELDs 1993
NJ	Toxic effuent limitations 24-hr avg. freshwater	0.013 µg/L	CELDs 1993
	Toxic effluent limitations saltwater	0.070	CELDs 199
	All saline classes - upper value	0.005 µ:g/L	EPA 1988b
NV	Aquatic use	0.00001 mg/L	CELDs 1993
OH	Warm water, outside mixing	0.005 µg/L	CELDs 1993
	zone,30-d avg	0.005 µg/L	CELDs 1993
	Warm water,human helth, 30-d avg.	0.0073 µg/L	CELDs 1993
	Aquatic life habitat: limited resource-cold water;outside mixing zone, 30-d avg	0.005 µ:g/L	CELDs 1993
	Aquatic life habitat: limited resource-cold and warm water, human health,30-d avg	0.0073 µg/L	CELDs 1993

OK	Acute	0.78 µg/L	CELDs 1993
	Chronic	0.0002 µg/L	CELDs 1993
	Fish and Wildife propagation	1.0 µg/L	EPA 1988b
OR	Acute-freshwater	0.78 µg/L	CELDs 1993
	Chronic-freshwater	0.0002 µg/L	CELDs 1993
	Marine-acute	0.21 µg/L	CELDs 1993
	Chronic-marine	0.0002 µg/L	CELDs 1993
PR	All coastal water classes upper value	0.005 µg/L	EPA 1988b
RI	Freshwater classes D and E		
	Upper level	1.6 & mu;g/L	EPA 1988b
	Secondary Classes -upper value	0.005 µg/L	EPA 1988b
	Saline Classes SA, SB and SC		
	Upper level	0.07 µg/L	EPA 1988b
SD	Acute	0.73 µg/L	CELDS 1993
	Chronic	0.0002 µg/L	CELDS 1993
TN	Continuous	0.002 µ/L	CELDs 1993
	Max	0.73 µ/L	CELDs 1993
TX	Chronic-freshwater	0.0002 µ/L	CELDs 1993
	Acute-freshwater	0.78 µ/L	CELDs 1993
	Acute-marine	0.21 µ/L	CELDs 1993
	Chronic-marine	0.0002 µ/L	CELDs 1993
UT	4-d avg.	0.0002 µ/L	CELDs 1993
	1-h avg.	0.73 µ/L	CELDs 1993
	Aquatic life classes 3A-D	0.005 µ/L	EPA 1988b
VA	Chronic-freshwater	0.013 µ/L	CELDs 1993
	Chronic-saltwater	0.0007 µ/L	CPA 1988b
VT	Acute	0.73 µ/L	CELDs 1993
	Chronic	0.0002 µ/L	CELDs 1993
WI	Acute-Great Lakes	0.61 µ/L	CELDs 1993
	Acute-Cold water	0.81 µ/L	CELDs 1993

	Acute-warm water spot fish	0.73 µ/L	CELDs 1993
	Acute-all others	0.81 µ/L	CELDs 1993
	Chronic-cold water	0.01 µ/L	CELDs 1993
	Warm water sport fish	0.01 µ/L	CELDs 1993
	All others	0.01 µ/L	CELDs 1993
	Water Quality: Propagation of Wildlife		
NV		0.005 mg/L	CELDs 1993
	Water Quality: Agricultural Use		
AZ	Irrigation	0.005 mg/L	CELDs 1993
	Livestock watering	0.005 mg/L	CELDs 1993
NV	Irrigation	0.005 mg/L	CELDs 1993
	Watering of livestock	0.00001 mg/L	CELDs 1993
OH		0.0071 µ/L	CELDs 1993
	Water Quality: Recreational Use		
AZ	Full body contact	3.0 µ/L	CELDs 1993
	Partial body contact	1000 µ/L	CELDs 1993
DC		0.01 µ/L	CELDs 1993
RI	Freshwater Classes B & C - upper value	1.6 µ/L	EPA 1988b
	Freshwater Classes B & C -secondary upper limit	0.013 µ/L	EPA 1988b
TN		0.008 µ/L	CELDs 1993
	Groundwater Quality Standards		
AZ	Dringing water protected use	0.005 mg/L	
CO		0.005 mg/L	
MA		0.005 mg/L	
MO		0.000071 µ/L	
NJ	GW1 (GW 2 & 3)	0.005 mg/L	

NC	GS waters	0.000031 mg/L	
OR	Human consumption	0.005 mg/L	
TN		0.005 mg/L	
UT		0.005 mg/L	
WI	Public health-enforcement std.	0.0007 µ/L	
	Public health-preventive action	0.00007 µ/L	
	Max. conc. for GW prtxn	0.005 mg/L	
	Groundwater Monitoring Parameters		
CO		0.005 mg/L	
IN		0.005 mg/L	
IL	Max conc.-hazardous waste facility std.	0.005 mg/L	
	Monitoring constitute	none	
LA	Max conc.-harzardous waste facility std.	0.005 mg/L	
	Monitoring constituent	none	
MN	Monitoring constituent	none	
	Max conc.-harzardous waste facility std.	0.005 mg/L	
MO	Max conc.-harzardous waste facility std.	0.005 mg/L	
NJ	Max level-hazardous waste facility std.		0.005 mg/L
TN			0.005 mg/L
VA	Monitoring constituent		none
WI	Monitoring constituent		none
	Max conc.-hazardous waste facility std.		0.005 mg/L
WV	Monitoring constituent		none

IL	Public and Food Processing Water	0.005 mg/L
CA	Resticted pesticides	none
WI	MCLG	0.00003 mg/L
CA	Discharge Limits	0.21 ng/L
WI	No qty>qty which remains after BATEA treatment or a lesser qty that provides an ample safety margin MCL in Drinking Water	
NE		0.005 mg/L
OR		0.005 mg/L
	Max allow concs for organochlorides & other persistent pesticides preservation of species dependent on water body)	
PR	Coastal estuarine waters Surface waters Ground waters	0.0002 mg/L 0.0002 mg/L 0.0002 mg/L
OK	Alert and Concern Levels in Fish Tissue	5.0 mg/kg(alert) 2.5 mg/kg(concern)
WI	Toxic Discharge	none
CA	Total Thershold Limit Conc. in Extremely Hazardous Wastes	500 mg/kg

CA	Persistent and Bioaccumulative Toxic Subatances and Their Total Thershold Limit Concentation for Extremely Hazardous Wastes	500 mg/kg (wt.-wt)
CA	Prohibition of Net Discharge Associated with Industrial,Toxic and Other Wastes	none
SD	Surface Water Discharge Permit Application Requirements: Test Requirements for Organic Toxic Pollutants	none
NJ	NPDES Permits: Testing Requirements for Organic Toxic Pollutants	none
c.Other:		
	Hazardous Waste	CELDs 1993
CA		none
NJ	Max level-hazardous waste	0.005 mg/L
CO		none(LDR)
IL		none
LA		none
MA		none(LDR)
ND		none
NH		none

WI	none
WV	none
WI	none

Hazardous Waste Toxicity Charecteristic

CA	0.5mg/L
CO	0.5mg/L
IL	0.5mg/L
LA	0.5mg/L
MA	0.5mg/L
MN	0.5mg/L
ND	0.5mg/L
PA	0.5mg/L
WI	0.5mg/L
WV	0.5mg/L

Hazardous Waste Constituents

CO	none
IL	none(App.H)
	none(App.G)
LA	none
MN	none
ND	none(App.IV)
WI	none

WV	none(App.VIII) none(App. VII)

NOTE: Update of drinking water guidelines and other areas in progress.
Units in table reflect values and units of measure designated by each agency in its regul
^{a} Probably carcinogenic to humans
ACGIH = American conference of Governmental and Industrial Hygienists; CAAA = Clean Air A
Chemical Emergency Preparedness Program;
CPSC = Consumer Product Safety Commission; EPA = Environmental Protection Agency; FSTRAC
International Agency for Research on
Cancer; IRIS = Integrated Risk Information System; LDR = Land Disposal Restriction; MCL =
available at the present time;
NATICH = National Air Taxics Information Clearinghouse; NIOSH = National Institute of Occ
System; NTP = National
Toxicology Program; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedi
Occupational Safety and Health
Administration; OSW = Office of Solid Waste; OW = Office of Water; PCB = Polychlorinated
TLV = Threshold Limit Value;
TSCA = Toxic Substances Control Act; TWA = Time Weighted Average; TWA = Time Weighted Ave

7-1. Regulations and Guidelines Applicable to Toxaphene

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption Coefficient (K_{oc}) -- The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd) -- The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the a mount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Bioconcentration Factor (BCF) -- The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Cancer Effect Level (CEL) – The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen – A chemical capable of inducing cancer.

Ceiling Value – A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure – Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles

Developmental Toxicity – The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse development effects may be detected at any point in the life span of the organism.

Embryotoxicity and Fetotoxicity – Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory – An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH) – The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

Intermediate Exposure – Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunologic Toxicity – The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals

In Vitro – Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo – Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC$_{LO}$) – The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LD$_{50}$) – A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD$_{LO}$) – The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50}) – The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50}) – The calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL) – The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malformations – Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level – An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effect over a specified duration of exposure.

Mutagen – A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity – The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) – The dose of chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow}) – The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Permissible Exposure Limit (PEL) – An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1^* – The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1^* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) – An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effect such as cancer.

Reportable Quantity (RQ) – The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity – The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Short-Term Exposure Limit (STEL) – The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

Target Organ Toxicity – This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen – A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV) – A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) – An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) – A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) – A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

Appendix A
User's Guide

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposures (LSE)

Tables (2-1, 2-2. and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and end point and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No- Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

LEGEND

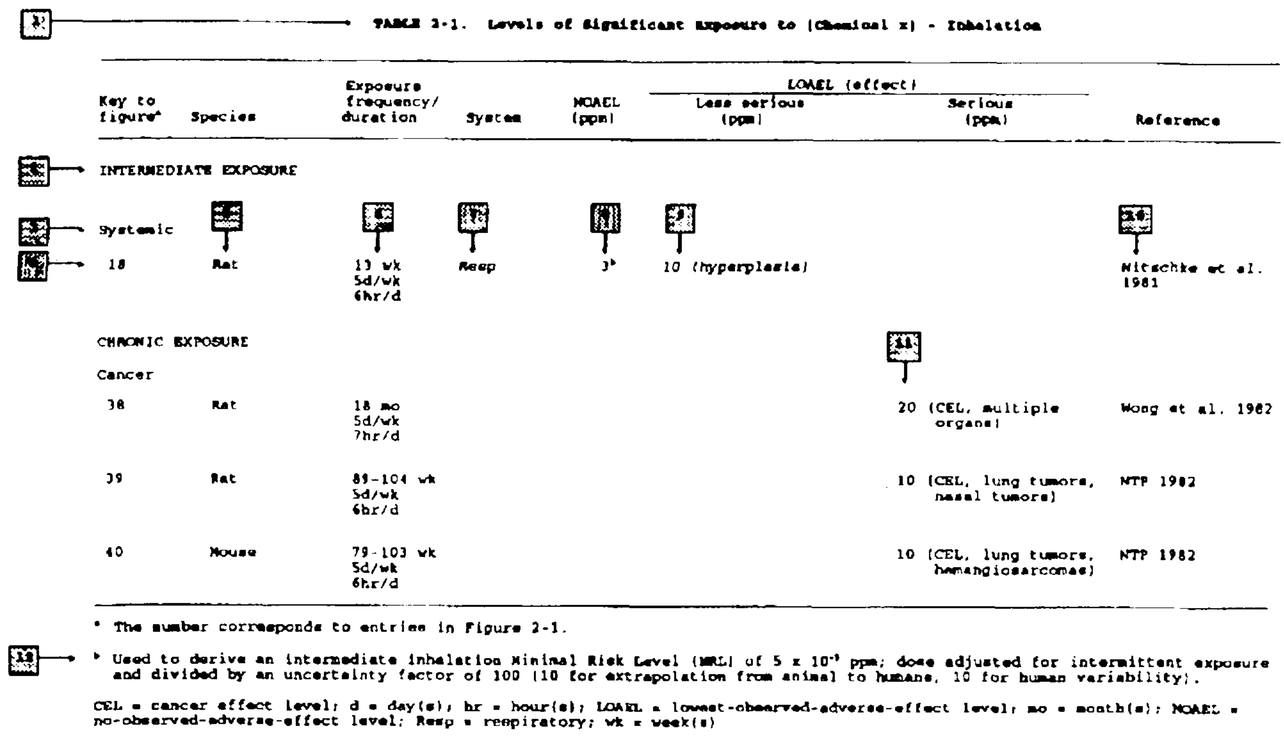


TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Systemic							
18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer							
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

LSE Table 2-1

(1).Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist, three LSE table and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.

(2).Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 days to 364 days); and chronic (365 days or more) and presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

(3).Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.

(4).Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-1).

(5).Species The test species, whether animal or human, are identified in this column.

(6).Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day

(7).System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "other" refers to any systemic effect (e.g. a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

(8).NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9).LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. a brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

(10).Reference The complete reference citation is given in Chapter 8 of the profile.

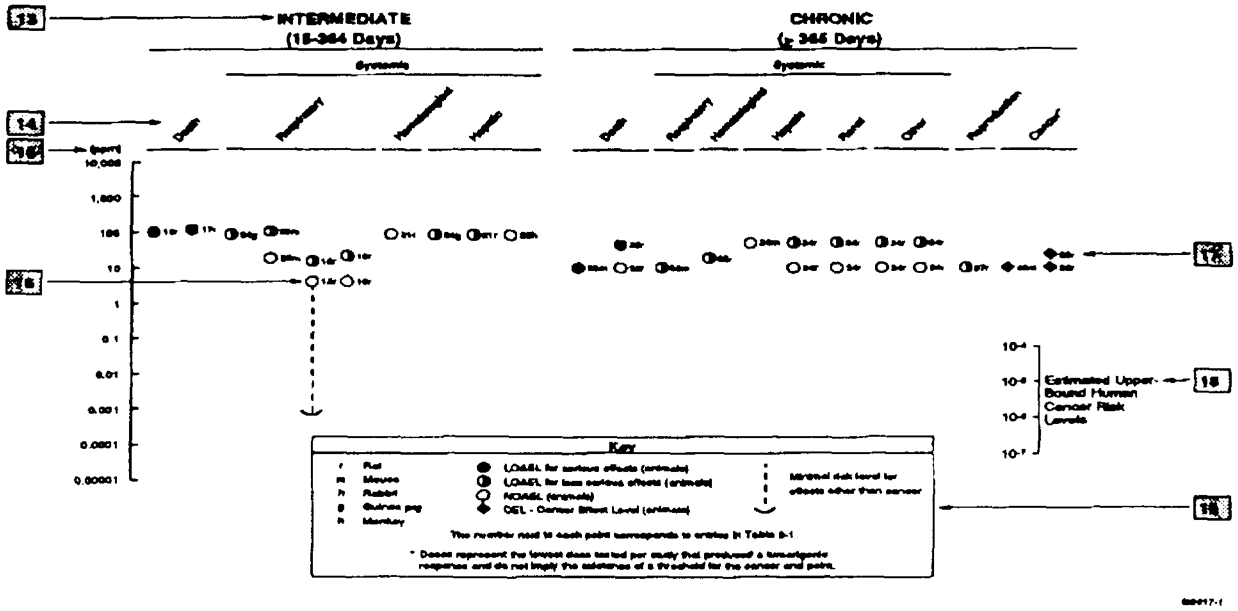
(11).CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.

(12).Footnotes explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

SAMPLE

FIGURE 2-1. Levels of Significant Exposure to [Chemical X] - Inhalation



LSE Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure levels for particular exposure duration.

(13). Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14). Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.

(15). Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16). NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17). CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table).

(18). Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q^1).

(19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency of perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate sections(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continuous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor of (1, 3, or 10) is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of (1, 3, or 10) are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and (1, 3, or 10) are used for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual MRL workgroup reserves the right to use uncertainty factors of (1, 3, or 10) based on scientific judgement. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Appendix B
Acronyms, Abbreviations, and Symbols

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
AML	acute myeloid leukemia
atm	atmpsphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United States
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
fpm	feet per minute
FR	Federal Register

g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	trans,trans-muconic acid
mCi	millicurie
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System

ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
PCE	polychromatic erythrocytes
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard morality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
UMDNJ	University of Medicine and Denistry New Jersey
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization

wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
µm	micron
µg	microgram

17 7 0732

TOXAPHENE:

BASIS FOR A CHANGE IN AND RECALCULATION OF THE CANCER POTENCY FACTOR

PREPARED BY:

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1313 North Market Street
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September 17, 1997

VOLUME II OF II

APPENDIX 4

PATHOLOGY WORKING GROUP PEER REVIEW OF NEOPLASTIC LESIONS IN THE LIVER IN B6C3F$_1$ MICE. AMENDED REPORT AND STATISTICAL ANALYSIS OF B6C3F$_1$ MOUSE LIVER TUMORS FOR TOXAPHENE

EPL®

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

BIOASSAY OF TOXAPHENE FOR POSSIBLE CARCINOGENICITY (NCI-CG-TR-37)

PATHOLOGY WORKING GROUP PEER REVIEW OF NEOPLASTIC LESIONS IN THE LIVER IN B6C3F1 MICE

CAS NO. 8001-35-2
AMENDED REPORT

Submitted to:

Hercules Incorporated
1313 N. Market Street
Wilmington, DE 19894-0001

Submitted by:

Experimental Pathology Laboratories, Inc.
P.O. Box 12766
Research Triangle Park, NC 27709

March 29, 1996

HERCULES INCORPORATED
RECEIVED
APR 03 1996
MEDICAL DEPARTMENT

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APPENDIX B
CURRICULA VITAE

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EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

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EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

BIOASSAY OF TOXAPHENE FOR POSSIBLE CARCINOGENICITY
(NCI-CG-TR-37)

PATHOLOGY WORKING GROUP PEER REVIEW OF NEOPLASTIC LESIONS IN THE LIVER IN B6C3F1 MICE

EPL PROJECT 172-004

AMENDED NARRATIVE SUMMARY

INTRODUCTION

A bioassay of technical-grade Toxaphene for possible carcinogenicity was conducted with B6C3F1 mice by administering the test chemical in feed by the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI). The technical report for this study was published by the NCI in 1979, Technical Report Series No. 37. The purpose of this review is to have a panel of experts examine all neoplastic lesions in the liver and provide a consensus diagnosis for each lesion examined using current diagnostic criteria and nomenclature. The initial evaluations were reported by the NCI in 1979 and have been recently reviewed by Drs. Ray Brown and John Cullen for Hercules, Inc.

Since the numbers of animals in the matched-control groups were small, pooled-control groups also were used by the NCI for statistical evaluation. For the mice, matched controls from the current bioassay were combined with matched controls from studies performed on lindane (CAS 58-89-9), malathion (CAS 121-75-5), phosphamidon (CAS 13171-21-6), and gardona (CAS 961-11-5) to give pooled-control groups consisting of 50 males and 50 females. A summary of the experimental design for the study is presented as follows:

Group No.	Compound Name	Dose	No. of Animals Males	 Females
1T*	Toxaphene	Vehicle Control	10	10
1G*	Gardona	Vehicle Control	10	10
1M*	Malathion	Vehicle Control	10	10
1L*	Lindane	Vehicle Control	10	10
1P*	Phosphamidon	Vehicle Control	10	10
2	Toxaphene	Low	50	50
3	Toxaphene	High	50	50

*The letters on the vehicle control groups coincide with the first letter of the compound.

Conduct of the Reviewing Pathologists' Examination

A reexamination of the hematoxylin and eosin stained histologic slides of male and female mouse livers was conducted independently by two pathologists, Drs. W. Ray Brown and John M. Cullen, for Hercules, Inc. The histopathologic criteria and nomenclature employed for proliferative lesions were based upon those recommended by the National Toxicology Program (Maronpot, et al., 1987). The final reports of these reexaminations were submitted to Hercules, Inc. on December 7, 1995 and December 15, 1995, respectively.

Conduct of the Pathology Working Group Review

The Pathology Working Group was chaired by Dr. Jerry F. Hardisty, Experimental Pathology Laboratories, Inc. (EPL®), who organized and presented the material to the panel of five pathologists. Curricula vitae for the PWG Chairperson and each of the PWG participants are present in Appendix B. The PWG review was performed on March 1, 1996 at the NTP Archives in the Research Triangle Park, NC. Individuals attending or participating in the PWG review are listed as follows:

Dr. Jerry F. Hardisty, Diplomate, A.C.V.P.	(PWG Chairperson)
Dr. Russell Cattley, Diplomate, A.C.V.P.	(PWG Participant)
Dr. Michael Elwell, Diplomate, A.C.V.P.	(PWG Participant)
Dr. Joel Leininger, Diplomate, A.C.V.P.	(PWG Participant)
Dr. E.E. McConnell, Diplomate, A.C.V.P., A.B.T.	(PWG Participant)
Dr. Jerrold Ward, Diplomate, A.C.V.P.	(PWG Participant)
Dr. Florence Kinoshita	(Observer)

The PWG examined coded slides without knowledge of treatment group. The PWG examined slides containing sections of liver with a previous diagnosis of an hepatocellular neoplasm or focal cellular alteration either reported by NCI in Technical Report No. 37 or by either of the Reviewing Pathologists. Each participant recorded his diagnoses and comments on worksheets which were prepared by the PWG Chairperson. The PWG examined the slides only for hepatocellular neoplasms or focal cellular alteration and did not consider other lesions which may have been present. Each lesion was discussed by the group, reexamined if necessary, and the final opinions were recorded on the Chairperson's worksheets. The consensus diagnoses of the PWG were reached when at least three of five PWG participants were in agreement.

The diagnostic criteria used to classify the proliferative hepatocellular lesions during this review was consistent with that currently proposed and used by the National Toxicology Program (Maronpot, et al., 1987). The terms and diagnostic criteria for each are summarized as follows:

Foci of Cellular Alteration

- Localized lesions with tinctorial variation from surrounding hepatic parenchyma
- Range from less than a hepatic lobule to up to three or four lobules in greatest dimension
- Merge with adjacent parenchyma without producing notable compression
- May be subclassified according to tinctorial variation into clear cell, eosinophilic, basophilic and mixed

Hepatocellular Adenoma

- Usually a discrete lesion that compresses adjacent parenchyma
- Composed of well-differentiated cells that may be eosinophilic, basophilic, or vacuolated
- Absence of normal hepatic lobular architecture within an adenoma

Hepatocellular Carcinoma

- Distinct trabecular or adenoid pattern
- Cells may be poorly differentiated or anaplastic
- May be histologic evidence of local invasion or metastasis

Hepatoblastoma

- Distinguished by basophilia with H&E stain
- Tumor cell arranged in several layers either radially or concentrically around endothelial-lined vascular spaces
- In some areas cells may be arranged in rows, rosettes, sheets, or ribbons
- Small, dark, oval or elongated cells
- Almost invariably found within or adjacent to hepatocellular neoplasms
- Usually sharply demarcated from the surrounding hepatocellular tumor tissue

The tissue sections for this study were prepared over 20 years ago. Due to the normal aging process of archived microscopic slides, several of the sections were not optimum for histopathologic examination. For some slides the mounting media for the coverslips had dried out, making microscopic examination difficult since some portions of the sections were obscured or the tinctorial quality of the stain was altered rendering the tissue faded and eosinophilic. In these instances the PWG provided a consensus diagnosis based on their best assessment of the material present.

The PWG's task was to confirm the presence or absence of a neoplasm or focal cellular alteration in the liver and to provide a consensus diagnosis for each lesion examined. The PWG did not attempt to interpret the study in terms of a "cause/effect". The PWG recorded hepatocellular adenoma, hepatocellular carcinoma, hepatoblastoma and/or cellular alteration, focal when present, but did not record multiple tumors of the same type or attempt to subclassify the cellular alteration due to the varying tinctorial quality of the tissue sections. Tumor multiplicity can only be determined when complete gross necropsy information is available and gross lesions are tracked from necropsy to the microscopic slide. Since the study was conducted prior to implementation of the Good Laboratory Practice Regulations, the PWG was concerned that the reliability of the gross observations may have been insufficient to determine tumor multiplicity for each animal in the study.

After the PWG completed the slide review and the diagnoses were recorded by the PWG Chairperson, the slides were decoded by treatment group. NCI diagnoses, Study Pathologists' diagnoses and PWG consensus diagnoses for individual animals reviewed in each group are presented in Appendix A. To assist in comparison among the different reviews, hepatocellular neoplasms diagnosed by the Reviewing

Pathologists were recorded as: hepatocellular carcinoma, hepatocellular adenoma, hepatoblastoma and hemangiosarcoma. Cellular alteration, focus/area was recorded as cellular alteration, focal.

Jerry F. Hardisty DVM
JERRY F. HARDISTY, D.V.M.
PWG Chairperson

March 29, 1996
Date

REFERENCE

Maronpot RR, Haseman JK, Boorman GA, Eustis SE, Rao GN, and Huff JE (1987) Liver Lesions in B6C3F1 Mice: The National Toxicology Program, Experience and Position. Arch. Toxicol., Suppl. 10, 10-26.

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EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

QUALITY ASSURANCE FINAL CERTIFICATION

Study Title: Bioassay of Toxaphene for Possible Carcinogenicity (NCI-CG-TR-37)

Client Study: CAS No. 8001-35-2 EPL Project Coordinator: Dr. Hardisty

EPL Project Number: 172-004 EPL Pathologist: Dr. Hardisty

The following aspects of this study were inspected by the Quality Assurance Unit of Experimental Pathology Laboratories, Inc. Dates inspections were performed and findings reported to the Project Coordinator and Management are indicated below.

	Dates	
Area Inspected	Inspection	Reporting
EPL Project Sheets	February 9, 1996	February 9, 1996
Project Setup	N/A	N/A
Histology Setup	N/A	N/A
Histology Complete	N/A	N/A
Rough Draft Report	March 4 & 5, 1996	March 5, 1996
Final Report	March 20, 1996	March 20, 1996
Data Review	February 27, 1996	February 27, 1996
Amended Report	March 29, 1996	March 29, 1996

Date of last quarterly facility inspection December, 1995

Jane J. Hollingsworth
EPL Quality Assurance Unit

March 29, 1996
Date

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REASON FOR CHANGE

The amended report is submitted to correct a typographical error on page 5 of the final report. The last three lines on page 5 were repeated at the top of page 6. The amended report deletes these three lines from page 5.

Jerry F. Hardisty DVM

JERRY F. HARDISTY, D.V.M.
PWG Chairperson

March 29, 1996
Date

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EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

APPENDIX A

PWG Consensus Diagnoses for Individual Animals Reviewed in Each Group

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 1G - Gardona (Vehicle Control) - Males

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
251	No Proliferative Lesion	Hepatocellular Adenoma	Basophilic Cellular Alteration, Focal	Cellular Alteration, Focal

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 1L - Lindane (Vehicle Control) - Males

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
092	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma Hepatocellular Adenoma	Hepatocellular Carcinoma Hepatocellular Adenoma
096	Neoplastic Nodule	Hepatocellular Adenoma	Mixed Cellular Alteration, Focal	Cellular Alteration, Focal
100	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 1M - Malathion (Vehicle Control) - Males

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
271	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	No Proliferative Lesion
274	No Proliferative Lesion	Eosinophilic Cellular Alteration, Focal	Eosinophilic Cellular Alteration, Focal	Cellular Alteration, Focal
279	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 1P - Phosphamidon (Vehicle Control) - Males

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
233	Hepatocellular Carcinoma	Hepatocellular Carcinoma Hemangiosarcoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma Hemangiosarcoma
235	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma
237	No Proliferative Lesion	Hemangiosarcoma	No Proliferative Lesion	Hemangiosarcoma

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 1T - Toxaphene (Vehicle Control) - Males

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
32	Neoplastic Nodule	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
35	Neoplastic Nodule	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
37	Cellular Alteration, Focal	Basophilic Cellular Alteration, Focal	Mixed Cellular Alteration, Focal	Cellular Alteration, Focal

PATHOLOGY WORKING GROUP CONSENSUS DIAGNOSES

8001-35-2

Group 2 - Toxaphene (Low) - Males

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
251	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma
252	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
253	Hepatocellular Carcinoma	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma, Multiple	Hepatocellular Adenoma Cellular Alteration, Focal
255	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma
256	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma
257	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma, Multiple	Hepatocellular Carcinoma
258	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma
259	Hepatocellular Carcinoma	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma Cellular Alteration, Focal
260	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 2 - Toxaphene (Low) - Males

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
261	Hepatocellular Carcinoma	Hepatocellular Adenoma Basophilic Cellular Alteration, Focal Eosinophilic Cellular Alteration, Focal	Mixed Cellular Alteration, Focal, Multiple Eosinophilic Cellular Alteration, Focal, Multiple	Cellular Alteration, Focal
262	Angiosarcoma	Angiosarcoma	Hemangiosarcoma	Hemangiosarcoma
263	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma Hepatocellular Adenoma	Hepatocellular Adenoma
264	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma Mixed Cellular Alteration, Focal	Hepatocellular Adenoma
265	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma Hepatoblastoma	Hepatocellular Adenoma Hepatcblastoma
267	Neoplastic Nodule	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
268	Neoplastic Nodule	Eosinophilic Cellular Alteration, Focal	Basophilic Cellular Alteration, Focal	Cellular Alteration, Focal
269	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hemangiosarcoma	Hepatocellular Adenoma

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 2 - Toxaphene (Low) - Males

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
270	Hepatocellular Carcinoma	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma, Multiple	Hepatocellular Adenoma
271	Neoplastic Nodule	Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma	Hepatocellular Adenoma
272	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma, Multiple	Hepatocellular Adenoma
273	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma
274	Hepatocellular Carcinoma	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal, Multiple	Hepatocellular Adenoma Cellular Alteration, Focal
275	Neoplastic Nodule	Hepatocellular Adenoma	Hepatocellular Adenoma	Cellular Alteration, Focal
276	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 2 - Toxaphene (Low) - Males

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
277	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma, Multiple Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma
280	No Proliferative Lesion	Eosinophilic Cellular Alteration, Focal	Eosinophilic Cellular Alteration, Focal Mixed Cellular Alteration, Focal Basophilic Cellular Alteration, Focal	Cellular Alteration, Focal
281	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma, Multiple Hepatocellular Adenoma, Multiple	Hepatocellular Carcinoma Hepatocellular Adenoma Cellular Alteration, Focal
282	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma
283	Neoplastic Nodule	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma
284	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma
285	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma Basophilic Cellular Alteration, Focal	Hepatocellular Adenoma Cellular Alteration, Focal

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 2 - Toxaphene (Low) - Males

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
286	Hepatocellular Carcinoma	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma, Multiple	Hepatocellular Adenoma Cellular Alteration, Focal
287	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
288	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma Hepatocellular Carcinoma, Multiple	Hepatocellular Adenoma
290	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma Hepatocellular Adenoma Basophilic Cellular Alteration, Focal	Hepatocellular Adenoma
292	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma
293	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
294	Neoplastic Nodule	Hepatocellular Adenoma	Hepatocellular Adenoma, Multiple	Hepatocellular Adenoma
295	Hepatocellular Carcinoma	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma, Multiple Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma Cellular Alteration, Focal

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 2 - Toxaphene (Low) - Males

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
296	Hepatocellular Carcinoma	Hepatocellular Adenoma Hepatocellular Carcinoma	Hepatocellular Carcinoma, Multiple Mixed Cellular Alteration, Focal Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma
299	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
300	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 3 - Toxaphene (High) - Males

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
351	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma, Multiple	Hepatocellular Adenoma
352	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
354	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma
355	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
356	Hepatocellular Carcinoma	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal	Hepatocellular Carcinoma	Hepatocellular Adenoma
357	Hepatocellular Carcinoma	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal	Hepatocellular Carcinoma, Multiple Mixed Cellular Alteration, Focal	Hepatocellular Adenoma Cellular Alteration, Focal
358	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma, Multiple	Hepatocellular Adenoma
359	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma
360	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma, Multiple	Hepatocellular Adenoma
361	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 3 - Toxaphene (High) - Males

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
362	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma, Multiple	Hepatocellular Adenoma
363	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma, Multiple	Hepatocellular Adenoma
364	Hepatocellular Carcinoma	Hepatocellular Adenoma	Mixed Cellular Alteration Focal, Multiple Eosinophilic Cellular Alteration, Focal, Multiple	Hepatocellular Adenoma Cellular Alteration, Focal
365	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
367	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma, Multiple Mixed Cellular Alteration, Focal	Hepatocellular Adenoma
368	Hepatocellular Carcinoma	Hepatocellular Adenoma Hepatocellular Carcinoma	Hepatocellular Adenoma Hepatocellular Carcinoma	Hepatocellular Adenoma Hepatocellular Carcinoma
369	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma
370	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma, Multiple	Hepatocellular Carcinoma

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 3 - Toxaphene (High) - Males

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
371	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma
372	Hepatocellular Carcinoma	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal	Mixed Cellular Alteration, Focal, Multiple	Hepatocellular Adenoma
373	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
374	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
375	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma
377	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma
378	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
379	Hepatocellular Carcinoma	Hepatocellular Adenoma Hepatocellular Carcinoma	Hepatocellular Adenoma Hepatocellular Carcinoma	Hepatocellular Adenoma
380	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma, Multiple	Hepatocellular Adenoma
381	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
382	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
383	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 3 - Toxaphene (High) - Males

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
384	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma
385	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal, Multiple	Hepatocellular Adenoma Cellular Alteration, Focal
386	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
387	Hepatocellular Carcinoma	Hepatocellular Adenoma	No Proliferative Lesion	Hepatocellular Adenoma
388	Hepatocellular Carcinoma	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma, Multiple Eosinophilic Cellular Alteration, Focal Mixed Cellular Alteration, Focal, Multiple	Hepatocellular Adenoma Cellular Alteration, Focal
389	Hepatocellular Carcinoma	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma Mixed Cellular Alteration, Focal, Multiple	Hepatocellular Adenoma Cellular Alteration, Focal
390	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma, Multiple	Hepatocellular Carcinoma

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 3 - Toxaphene (High) - Males

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
391	Hepatocellular Carcinoma	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma	Hepatocellular Adenoma
392	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma
395	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma
396	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
397	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
398	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
399	Hepatocellular Carcinoma	Hepatocellular Adenoma Angiosarcoma	Hepatocellular Carcinoma	Hepatocellular Adenoma Hemangiosarcoma
400	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 1L - Lindane (Vehicle Control) - Females

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
085	Neoplastic Nodule	Eosinophilic Cellular Alteration, Focal	Basophilic Cellular Alteration, Focal	Hepatocellular Adenoma

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 2 - Toxaphene (Low) - Females

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
201	Neoplastic Nodule	Hepatocellular Adenoma	Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma
202	Neoplastic Nodule	Hepatocellular Adenoma	Mixed Cellular Alteration, Focal	Hepatocellular Adenoma
208	Neoplastic Nodule	Eosinophilic Cellular Alteration, Focal	Eosinophilic Cellular Alteration, Focal	Cellular Alteration, Focal
210	No Proliferative Lesion	Eosinophilic Cellular Alteration, Focal	Eosinophilic Cellular Alteration, Focal	Cellular Alteration, Focal
212	Neoplastic Nodule	Hepatocellular Adenoma	Hepatocellular Adenoma Mixed Cellular Alteration, Focal	Hepatocellular Adenoma Cellular Alteration, Focal
214	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
216	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
217	Hepatocellular Carcinoma	Eosinophilic Cellular Alteration, Focal	Mixed Cellular Alteration, Focal	Cellular Alteration, Focal
219	Neoplastic Nodule	Hepatocellular Adenoma Basophilic Cellular Alteration, Focal	Hepatocellular Adenoma Basophilic Cellular Alteration, Focal	Hepatocellular Adenoma

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 2 - Toxaphene (Low) - Females

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
221	Hepatocellular Carcinoma	Hepatocellular Adenoma Tumor, NOS, Metastatic	Hepatocellular Adenoma	Hepatocellular Adenoma
222	Neoplastic Nodule	Eosinophilic Cellular Alteration, Focal	Mixed Cellular Alteration, Focal	Hepatocellular Adenoma
224	Neoplastic Nodule	Eosinophilic Cellular Alteration, Focal	Eosinophilic Cellular Alteration, Focal	Cellular Alteration, Focal
238	Hepatocellular Carcinoma	Eosinophilic Cellular Alteration, Focal	Basophilic Cellular Alteration, Focal	Cellular Alteration, Focal
241	Neoplastic Nodule	Hepatocellular Adenoma	Eosinophilic Cellular Alteration, Focal	Cellular Alteration, Focal
242	Neoplastic Nodule	Eosinophilic Cellular Alteration, Focal	Basophilic Cellular Alteration, Focal	Cellular Alteration, Focal
244	Neoplastic Nodule	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
245	Neoplastic Nodule	Eosinophilic Cellular Alteration, Focal	Basophilic Cellular Alteration, Focal	Cellular Alteration, Focal
246	Neoplastic Nodule	Eosinophilic Cellular Alteration, Focal	Hepatocellular Adenoma	Hepatocellular Adenoma

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 2 - Toxaphene (Low) - Females

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
247	Neoplastic Nodule	Basophilic Cellular Alteration, Focal Eosinophilic Cellular Alteration, Focal	Basophilic Cellular Alteration, Focal	Hepatocellular Adenoma

PATHOLOGY WORKING GROUP
CONSENSUS DIAGNOSES

8001-35-2

Group 3 - Toxaphene (High) - Females

Animal No.	NCI Diagnosis	Dr. W. Ray Brown	Dr. John M. Cullen	PWG Consensus
301	Neoplastic Nodule	Mixed Cellular Alteration, Focal	Hepatocellular Adenoma	Hepatocellular Adenoma
303	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Carcinoma, Multiple	Hepatocellular Adenoma
304	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
305	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma	Hepatocellular Adenoma
306	Hepatocellular Carcinoma	Hepatocellular Adenoma Eosinophilic Cellular Alteration, Focal	Hepatocellular Carcinoma Hepatocellular Adenoma	Hepatocellular Adenoma
308	No Proliferative Lesion	Mixed Cellular Alteration, Focal	Mixed Cellular Alteration, Focal	Cellular Alteration, Focal
309	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma, Multiple	Hepatocellular Adenoma
310	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma, Multiple	Hepatocellular Adenoma
312	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma	Hepatocellular Carcinoma
313	Hepatocellular Carcinoma	Hepatocellular Adenoma	Hepatocellular Adenoma, Multiple	Hepatocellular Adenoma

APPENDIX B

Curricula Vitae

EPL®

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

JERRY F. HARDISTY
VETERINARY PATHOLOGIST

EDUCATION:

Iowa State University, Pre-Veterinary, 1965-1967.
Iowa State University, D.V.M., 1971.

Certified by the American College of Veterinary Pathologists, 1976
Adjunct Associate Professor at the School of Veterinary Medicine, NC State University, 1983

PRESENT POSITION AND EXPERIENCE:

1994-Present. Vice President, Operations, Experimental Pathology Laboratories, Inc., Research Triangle Park, North Carolina.

Responsible for overall management and direction of pathology research laboratories in North Carolina and Virginia.

1978-1994. Director and Pathologist, Experimental Pathology Laboratories, Inc., Research Triangle Park, North Carolina.

Responsible for the project management, direction and technical supervision of the North Carolina branch of EPL. Responsible for the microscopic evaluation of tissues from experimental animals used in a variety of toxicological studies. Responsible for the National Toxicology Program's Pathology Quality Assessment Program and Operations of the NTP Archives.

1976-1978. Pathologist/Project Manager, Experimental Pathology Laboratories, Inc., Herndon, Virginia.

Responsible for the management of EPL's Carcinogenesis Support Laboratory. Project Manager of a program to provide Tracor Jitco with Quality Assurance in the NCI Carcinogenesis Testing Program. Technical supervision of a program to provide pathology support services to

1976-1978 - Continued   the Carcinogenesis Program of the National Cancer Institute. Responsible for the microscopic evaluation of tissues from experimental animals used in a variety of toxicological studies.

1972-1976.   Research Pathologist, Veterinary Pathology Branch, Biomedical Laboratory, Edgewood Arsenal, Maryland.

Dr. Hardisty was a preceptee in the U.S. Army preceptorship program in Veterinary Pathology. During this time he performed gross and microscopic diagnoses of spontaneous disease and changes produced by experimental procedures in laboratory animals. He prepared reports describing and interpreting these experimental results.

During this time he was principal investigator for the reproductive, mutagenic, teratogenic studies performed at the laboratory. This work consisted of revising previous experimental protocols and designing new experimental protocols to be utilized at the laboratory. The experimental design employed required the gross examination of pregnant female rats and fetuses for evidence of fetal toxicity and teratogenesis. He trained biological technicians to perform timed matings in rats, examine serially sectioned fetuses for malformations, and to examine fetal skeletons for prenatal abnormalities.

1971-1972.   Attending Veterinarian, Division of BioSensor Research, Walter Reed Army Institute of Research.

Dr. Hardisty studied the radiographic and morphologic lesions of several musculoskeletal diseases of the German Shepherd dog. In association with Dr. Wayne Riser, he investigated the pathogenesis and possible genetic relationship of canine hip dysplasia, eosinophilic panosteitis, and ununited anconeal processes in an attempt to reduce their incidence through a selective breeding program.

JERRY F. HARDISTY, D.V.M. - Continued

PROFESSIONAL MEMBERSHIPS:

Diplomate, American College of Veterinary Pathologists
Society of Toxicology
Society of Toxicologic Pathologists
North Carolina Veterinary Medical Association
International Academy of Pathology
American Veterinary Medical Association
American Animal Hospital Association
Charles Louis Davis, D.V.M. Foundation
The Society of Phi Zeta
The Society of Gamma Sigma Delta
The Fraternity of Alpha Zeta
The Fraternity of Omega Tau Sigma
American Association for the Advancement of Science

PROFESSIONAL ACTIVITIES:

Standard System of Nomenclature and Diagnostic Criteria (SSNDC), The Society of Toxicologic Pathologists, 1987-1995.

Councillor, The Society of Toxicologic Pathologists, 1994-1998.

Joint Committee for STPs/ILSI on International Standardization of Nomenclature and Diagnostic Criteria for Toxicologic Pathology, 1994-1995, Co-Chairman 1995-Present.

EDITORIAL REVIEW BOARD:

International Agency for Research on Cancer (WHO), Classification of Rodent Tumors, Part II, The Mouse, 1995-Present.

JERRY F. HARDISTY, D.V.M. - Continued

PUBLICATIONS AND PAPERS:

Factors predisposing to urolithiasis in feedlot cattle. Hardisty, J.F. and Dillman, R.C., The Iowa State University Veterinarian, Iowa State University, Ames, Iowa, 33(2), 77-81, 1971.

Reduction of frequency of hip dysplasia in military dogs. Riser, W.H., Hardisty, J.F., and Castleberry, M.W., *In Proceedings*, Canine Hip Dysplasia Symposium and Workshop, OFA, Columbia, MO., 1972.

Genetic influence of the male on the incidence of canine hip dysplasia. Hardisty, J.F., Scalera, S.E., Castleberry, M.W., and Riser, W.H., *In Proceedings*, Canine Hip Dysplasia Symposium and Workshop, OFA, Columbia, Mo., 1972.

Evaluation of the effects of chemical compounds on the reproductive system of rats. Hardisty, J.F., presented at the Biomedical Laboratory Review and Analysis, April 1975.

Reproductive studies with quint essence compounds. Hardisty, J.F., presented at the Biomedical Laboratory Review and Analysis of Quint Essence, January 1976.

Effects of KZ/IP mixture on the reproductive system. Hardisty, J.F. and Pellerin, R.J., Edgewood Arsenal Technical Report, 1976.

Reproductive studies with diisoproplymethylphosphate in rats. Hardisty, J.F., Pellerin, R.J., Biskup, R.F., and Manthei, J.H., Edgewood Arsenal Technical Report ARCSL TR 77037, May 1977.

Quality assurance in pathology. Hardisty, J.F., Ward, J.M., and Griesemer, R.A., NCI-NCTR Pathology Workshop, Bethesda, Maryland, June 1978.

Mononuclear cell leukemia in Fischer 344 rats. Hardisty, J.F., NCI-NCTR Pathology Workshop, Bethesda, Maryland, June 1978.

Quality assurance for pathology in rodent carcinogenesis tests. Ward, J.M., Goodman, D.G., Griesemer, R.A., Hardisty, J.F., Schueler, R.L., Squire, R.A., and Strandberg, J.D., Journal of Environmental Pathology and Toxicology, 2, 371-378, Nov.-Dec. 1978.

JERRY F. HARDISTY, D.V.M. - Continued

PUBLICATIONS AND PAPERS - Continued

Neoplasms and pigmentation of the thyroid gland in F-344 rats exposed to 2,4-diaminoanisole sulfate, a hair dye component. Ward, J.M., Stinson, S.F., Hardisty, J.F., Cockrell, B.Y., and Hayden, D.W., Journal of the National Cancer Institute, Vol. 62, No. 4, April 1979.

The carcinogenic and nephrotoxic effects of the flame retardant TRIS [(2,3-dibromopropyl) phosphate] in F-344 rats and B6C3F1 mice. Reznik, G., Ward, J.M., Hardisty, J.F., and Russfield, A., Journal of the National Cancer Institute, Vol. 63, No. 1, July 1979.

Correlation between gross observations of tumors and neoplasms diagnosed microscopically in carcinogenesis bioassays in rats. Kulwich, B.A., Hardisty, J.F., Gilmore, C.E., and Ward, J.M., Journal of Environmental Pathology and Toxicology, 3, 281-287, December 1979.

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JERRY F. HARDISTY, D.V.M. - Continued

PUBLICATIONS AND PAPERS - CONTINUED

Lesions of the rodent liver. Hardisty, J.F. Presented at the Dose Response Relationships for Hepatocarcinogenesis in Medaka Exposed to Waterbone N-Nitrosodietylamine Workshop on December 15, 1993.

Procedures for peer review in toxicologic pathology. Hardisty, J.F. Presented at the Society of Toxicologic Pathologists 13th International Symposium on June 5-9, 1994.

Necropsy and histology in toxicologic pathology. Hardisty, J.F. Presented at Industrial Toxicologic Pathology, University of Illinois at Urbana-Champaign, July 27, 1994.

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Neoplastic lesions of questionable significance. Hardisty, J.F. Presented at the 1994 Toxicologic Roundtable on October 3, 1994.

Use of nasal diagrams to record nasal lesions. Hardisty, J.F. Presented at the 1994 Toxicology Roundtable on October 4, 1994.

Morphologic assessment of pathologic changes in the rat larynx. Hardisty, J.F. Presented at the 1994 Toxicology Roundtable on October 4, 1994.

Pathology peer review and PWG. Hardisty, J.F. Presented at the 1995 Toxicology Roundtable in Nashville, Tennessee on October 23, 1995.

JERRY F. HARDISTY, D.V.M. - Continued

PUBLICATIONS AND PAPERS - CONTINUED

Computerized pathology data - summary vs. individual. Hardisty, J.F. Presented at the 1995 Toxicology Roundtable in Nashville, Tennessee on October 24, 1995.

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EDUCATION

1974	B.S., Rutgers University
1976	M.S., Clemson University
1980	V.M.D., University of Pennsylvania
1988	Ph.D., University of North Carolina

PROFESSIONAL LICENSURE AND CERTIFICATION

1980	Licensed Veterinarian in Pennsylvania
1984	Veterinary Pathologist, American College of Veterinary Pathologists

EXPERIENCE

1990-present	Scientist, Department of Experimental Pathology and Toxicology (1990-1995), Chemical Industry Institute of Toxicology, Research Triangle Park, NC (Acting Department Head, 1993-1995); Cancer Program, Associate Manager (1995-present)
1988-1990	Assistant Professor, Department of Microbiology, Pathology and Parasitology, College of Veterinary Medicine, and Member, Toxicology Graduate Faculty, North Carolina State University, Raleigh, NC
1986-1988	Postdoctoral Trainee, Chemical Industry Institute of Toxicology, Research Triangle Park, NC
1983-1988	Graduate student in pathology, University of North Carolina at Chapel Hill. Advisor: Dr. James A. Popp, Chemical Industry Institute of Toxicology, Research Triangle Park, NC. Dissertation title: Peroxisome Proliferator Hepatocarcinogenesis in Rats.
1980-1983	Resident in veterinary and comparative pathology. Training jointly conducted by University of Alabama in Birmingham School of Medicine and Dentistry and Auburn University School of Veterinary Medicine, sponsored by NIH

PROFESSIONAL DEVELOPMENT COURSES

-Computational Molecular Biology, Carolina Workshop, University of North Carolina, Chapel Hill, NC (1995)
-Designing and Installing Self-Directed Teams, Industrial Extension Service, North Carolina State University, Raleigh, NC (1994)
-Nucleic Acid Techniques, Carolina Workshop, University of North Carolina, Chapel Hill, NC (1993)
-Improving Managerial Skills of the New or Prospective Manager, American Management Association, Boston, MA (1993)
-Project Management, Applied Management Associates, Research Triangle Park, NC (1991)
-Physiologically-Based Pharmacokinetic Models - Principles and Implementation, CIIT, Research Triangle Park, NC (1991)

PROFESSIONAL AFFILIATIONS

American Association for Cancer Research
American Veterinary Medical Association
American College of Veterinary Pathologists
North Carolina Society of Toxicology
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AWARDS AND HONORARIES

1985	Individual National Research Service Award, NIH-NCI
1982	C.L. Davis Scholarship in Veterinary Pathology
1979	Phi Zeta (Veterinary Medical Honorary)
1977-79	N.J. Veterinary Education Foundation Scholarship

ACADEMIC AFFILIATIONS

1990-present	Adjunct Assistant Professor; Adjunct Associate Professor (1994-present): Department of Microbiology, Pathology, and Parasitology, College of Veterinary Medicine, North Carolina State University, Raleigh, NC. Member, Faculty Search Committee for Toxicologic Pathologists, N.C. State University (1994-1995).
1995-present	Adjunct Assistant Professor, Department of Pathology, School of Medicine, University of North Carolina, Chapel Hill, NC.
1995-present	Adjunct Assistant Professor, School of the Environment, Duke University, Durham, NC.

GRADUATE STUDENT COMMITTEES

Student	Institution	Degree	Date Comp.	Advisor(s)
Evan Gallagher	Duke University	Ph.D.	1991	R. DiGiulio
Glenda Moser	NC State University	Ph.D.	1993	R. Smart
Stephen Stefanski	NC State University	Ph.D.	1993	T. Brown M. Anderson

Richard Miller	NC State University	Ph.D	1994	J. Cullen J. Popp
Dave Watson	Duke University	Ph.D.	1995	R. DiGiulio
Heidi Bojes	UNC-CH	Ph.D.	1995	R. Thurman
Tae-Won Kim	NC State University	Ph.D.	In Progress	R. Smart
Stephen Ploch	Duke University	Ph.D.	In Progress	R. DiGiulio

COURSE INSTRUCTION

Year(s)	Institution	Course	Topic	Hours/Yr.
1989-1995 inclusive	NCSU	VMM 841 Systemic	Pathology of Liver, Pancreas and Peritoneum	5
1993	NCSU	VMS 590L Environmental Cell Biology	Hepatocarcinogenesis by Non-Genotoxic Chemicals	1
1992-1995 inclusive	UNC-CH	Pharm/Tox 207 Advanced Toxicology	Hepatic Structure and Function (1992-1995); Response of the Liver to Injury (1993); Coordinator, Hepatic Toxicity Section (1993-1995)	1-2
1993	Univ. Alabama-Birmingham	PAT 723 In Vivo Models of Human Disease	Animal Models in Carcinogenesis Research and Testing	1
1993, 1991, 1989	NCSU	VMS 642 Advanced Systemic Histopathology	Hepatic Pathology	2
1994, 1992, 1990, 1988	NCSU	VMS 643 Toxicologic Pathology	Gastrointestinal Pathology (1994); Course director (1988-1994)	1

ADVISORY APPOINTMENTS

1995	Member, Program Committee, International Life Sciences Institute Meeting on Peroxisome Proliferators, Washington, DC.
1994	Reviewer, Technical Report on Toxicity Studies of Dibutyl Phthalate, National Toxicology Program, Research Triangle Park, NC

1994	Reviewer, Pathology Services Contracts, National Toxicology Program, Research Triangle Park, NC
1994	Reviewer, W.H.O. Environmental Health Criteria document for dibutyl phthalate, Geneva, Switzerland
1993	Reviewer, Priority Substances List Assessment Report, Di(2-ethyhexyl)phthalate, Canadian Environmental Protection Act, Ottawa, Ontario
1992	Participant, U.S.E.P.A. Workshop on the Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health, Bethesda, MD
1991-present	Member, Project Advisory Committee, American Water Works Association Research Foundation, Denver, CO.
1991	Member, W.H.O. Task Group on Environmental Health Criteria for Di(2-ethylhexyl)phthalate, Carshalton, UK
1989	Participant, U.S.E.P.A. Carcinogen Assessment Group for di(2-ethylhexyl)phthalate, Bethesda, MD
1988-present	Reviewing Pathologist, Pathology Working Groups, National Toxicology Program, Research Triangle Park, NC.

AREAS OF INTEREST

Chemical *carcinogenesis and toxicologic pathology.*

PUBLICATIONS

1. Miller, R.T., Glover, S.E., Stewart, W.S., Corton, J.C., Popp, J.A., and Cattley, R.C.: "Effect on the expression of *c-met*, *c-myc*, and PPAR in liver and liver tumors from rats chronically exposed to the hepatocarcinogenic peroxosime proliferator WY-14,643," Carcinogenesis, in press (1996).

2. Miller, R.T., Shah, R.S., Cattley, R.C., and Popp, J.A.: "The peroxisome proliferators Wy-14,643 and methylclofenapate induce hepatocyte ploidy alterations and ploidy-specific DNA synthesis in F344 rats," Toxicol. Appl. Pharmacol., in press (1996).

3. Sausen, P.J., Teets, V.J., Voss, K.S., Miller, R.T., and Cattley, R.C.: "Gemfibrozil-induced peroxisome proliferation and hepatomegaly in male F344 rats," Cancer Lett. 97:263-268 (1995).

4. Sausen, P.J., Lee, D.C., Rose, M.L., and Cattley, R.C.: "Elevated 8-hydroxydeoxyguanosine in hepatic DNA of rats following exposure to peroxisome proliferators: Relationship to mitochondrial alterations," Carcinogenesis 16:1795-1801 (1995).

5. Miller, R.T., Cattley, R.C., Marsman, D.S., Lyght, O., and Popp, J.A.: "TGFα is differentially expressed in liver foci induced by diethylnitrosamine initiation and peroxisome proliferator promotion," Carcinogenesis 16:77-82 (1995).

6. Cattley, R.C., Kato, M., Popp, J.A., Teets, V.J., and Voss, K.S.: "Initiator-specific promotion of hepatocarcinogenesis by WY-14,643 and clofibrate," Carcinogenesis 15:1763-1766 (1994).

7. Cattley, R.C., Everitt, J.I., Gross, E.A., Moss, O.R., Hamm, T.E., Jr., and Popp, J.A.: "Carcinogenicity and toxicity of inhaled nitrobenzene in B6C3F1 mice and F344 and CD rats," Fundam. Appl. Toxicol. 22:328-340 (1994).

8. Cattley, R.C., and Glover, S.E.: "Elevated 8-hydroxydeoxyguanosine in hepatic DNA of rats following exposure to peroxisome proliferators: Relationship to carcinogenesis and nuclear localization," Carcinogenesis 14:2495-2499 (1993).

9. Murkofsky, R.L., Glover, S.E., Miller, R.T., Popp, J.A., and Cattley, R.C.: "Effect of regeneration and hyperplasia on levels of DNA base oxidation in rat liver," Cancer Lett. 70:51-56 (1993).

10. Kato, M., Popp, J.A., Conolly, R.B., and Cattley, R.C.: "Relationship between hepatocyte necrosis, proliferation and initiation induced by diethylnitrosamine in the male F344 rat," Fundam. Appl. Toxicol. 20:155-162 (1993).

11. Keller, B.J., Bradford, B.U., Marsman, D.S., Cattley, R.C., Popp, J.A., Bojes, H.K., and Thurman, R.G.: "The nongenotoxic hepatocarcinogen Wy-14,643 is an uncoupler of oxidative phosphorylation *in vivo*," Toxicol. Appl. Pharmacol. 119:52-58 (1993).

12. Castellino, S., Elion, G.B., Griffith, O.W., Dewhirst, M., Kurtzberg, J., Cattley, R.C., Scott, P., Bigner, D.D., and Friedman, H.S.: "Development of a model of melphalan-induced gastrointestinal toxicity in mice," Cancer Chemother. Pharmacol. 31:376-380 (1993).

13. Laskowitz, D.T., Elion, G.B., Dewhirst, M.W., Griffith, O.W., Cattley, R.C., Bigner, D.D., and Friedman, H.D.: "Enhancement of melphalan-induced gastrointestinal toxicity in mice treated with regional hyperthermia and BSO-mediated glutathione depletion," Int. J. Hyperthermia 8(1):111-20 (1992).

14. Gallagher, E.P., Cattley, R.C., and DiGiulio, R.T.: "The acute toxicity and sublethal effects of chlorothalonil in channel catfish (Ictalurus punctatus)," Chemosphere 24(1), 3-10 (1992).

15. Cattley, R.C., Marsman, D.S., and Popp, J.A.: "Age-related susceptibility to the carcinogenic effect of the peroxisome proliferator WY-14,643 in rat liver," Carcinogenesis 12:469-473 (1991).

16. Cattley, R.C., Deitze, S.R., Richardson, F.C., and Popp, J.A.: "Detection of 5-hydroxymethyl-2'-deoxyuridine in DNA from calf thymus, Hela cells, and rat liver nuclei," Nucleosides and Nucleotides 9:179-187 (1990).

17. Cattley, R.C., and Popp, J.A.: "Differences between the promoting activities of the peroxisome proliferator WY-14,643 and phenobarbital in rat liver," Cancer Res. 49:3246-3251 (1989).

18. Conway, J.G., Cattley, R.C., Popp, J.A., and Butterworth, B.E.: "Possible mechanism in hepatocarcinogenesis by the peroxisome proliferator di(2-ethylhexyl)phthalate," Drug. Metab. Rev. 21(1):65-102 (1989).

19. Conway, J.G., Tomaszewski, K.E., Olson, M.J., Cattley, R.C., Marsman, D.S., Melnick, R.L., and Popp, J.A.: "Relationship of oxidative damage to hepatocarcinogenicity of the peroxisome proliferators di(2-ethylhexyl)phthalate and WY-14,643," Carcinogenesis 10:513-519 (1989).

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21 Cattley, R.C., Smith-Oliver, T., Butterworth, B.E., and Popp, J.A.: "Failure of the peroxisome proliferator WY-14,643 to induce unscheduled DNA synthesis in rat hepatocytes following in vivo treatment," Carcinogenesis 9:1179-1183 (1988).

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25. Popp, J.A., Garvey, L.K., and Cattley, R.C.: "In vivo studies on the mechanism of di(2-ethylhexyl)phthalate carcinogenesis," Toxicol. Indust. Health 3:151-163 (1987).

26. Cattley, R.C., Richardson, K.K., Smith-Oliver, T., Popp, J.A., and Butterworth, B.E.: "Effect of peroxisome proliferator carcinogens on unscheduled DNA synthesis in rat hepatocytes determined by autoradiography," Cancer Lett. 33:269-277 (1986).

27. Easley, J.R., Meuten, D.J., Levy, M.G., Dykstra, M.J., Breitschwerdt, E.B., Holzinger, E.A., and Cattley, R.C.: "Nasal rhinosporidiosis in the dog," Vet. Pathol. 23:50-56 (1986).

28. Butterworth, B.E., Bermudez, E., Smith-Oliver, Earle, L., Cattley, R.C., Martin, J., Popp, J.A., Strom, S., Jirtle, R. and Michalopoulos, G.: "Lack of genotoxic activity of di(2-ethylhexyl)phthalate (DEHP) in rat and human hepatocytes," Carcinogenesis 5:1329-1335 (1984).

29. Cattley, R.C., and Barnett, B.D.: "The effect of pokeberry ingestion on immune response in turkeys," Poultry Science 56:246-248 (1977).

30. Cattley, R.C., Jones, J.E., and Barnett, B.D.: "Inefficacy of aspirin in reducing broodiness in turkeys," Poultry Science 55:12997-1998 (1976).

Book Chapters

1. Cattley, R.C., Miller, R.T., and Corton, J.C.: "Peroxisome proliferators: Potential role of altered hepatocyte growth and differentiation in tumor development." In: Growth Factors and Tumor Promotion: Implication for Risk Assessment (Prog. Clin. Biol. Res.). Wiley-Liss, New York, pgs. 295-303 (1995).

2. Popp, J.A., Cattley, R.C., Miller, R.T., and Marsman, D.S.: "Relationship of peroxisome proliferator induced cellular effects to hepatocarcinogenesis." In: Receptor-Mediated Biological Processes: Implications for Evaluating Carcinogenesis [Prog. Clin. Biol. Res., Vol. 387], pgs. 193-207 (1994).

3. Popp, J.A., and Cattley, R.C.: "Peroxisome proliferators as initiators and promoters of rodent hepatocarcinogenesis." Monograph on Peroxisome Proliferation, Gibson and Lake, eds., Taylor and Francis, Ltd., pp. 653-665. (1993).

4. Popp, J.A., Cattley, R.C.: Hepatobiliary System. In: Fundamentals of Toxicologic Pathology. W. Haschek, C. Rousseux, eds. Academic Press, Inc., San Diego, CA, pp. 279-314 (1991).

5. Cattley, R.C., Marsman, D.S., and Popp, J.A.: "Cell proliferation and promotion in the hepatocarcinogenicity of peroxisome proliferating chemicals." In: Mutation and the Environment. Part D. Carcinogenesis. M.L. Mendelsohn and R.J. Albertini, eds., Wiley-Liss, New York, pp. 123-132 (1990).

Abstracts

1. Miller, R.T., and Cattley, R.C.: "Microscopic features of regressing peroxisome proliferator-induced hepatocellular adenomas," Vet. Pathol. 32:599 (1995).

2. Miller, R.T., Glover, S.E., Stewart, W.S., Corton, J.C., Popp, J.A., and Cattley, R.C.: "Effect on the expression of c-met, c-myc, and PPAR in liver and liver tumors from rats chronically exposed to the hepatocarcinogenic peroxisome proliferator WY-14,643," Toxicol. Pathol. 23:759 (1995).

3. Bojes, H.K., Sausen, P.J., Cattley, R.C., and Thurman, R.G.: "KCN insensitive respiration following dietary exposure to WY-14,643 (WY)," Toxicologist 15:239 (1995).

4. Sumner, S.C., Asgharian, B., Moss, O., Cattley, R.C., and Fennell, T.R.: "Correlating styrene metabolism and distribution with hepatotoxicity," Toxicologist 15:4 (1995).

5. Stalker, M.J., Cattley, R.C., Quinn, B.A., and Hayes, M.A.: "Oxidative DNA damage and antioxidant enzyme activities during progression of liver neoplasms in rats," Proc. Am. Assoc. Cancer Res. 36:165 (1995).

6. Sumner, S.J., Asgharian, B., Moss, O., Youtsey, N.L., Cattley, R.C., and Fennell, T.R.: "The metabolism, distribution, and hepatotoxicity of styrene in F344 rats, B6C3F1 mice, and CD1 mice following single and repeated inhalation exposures," ISSX Proceedings 6:280 (1994).

7. Corton, J.C., Merritt, A., Anderson, S., Miller, R., Sausen, P., and Cattley, R.C.: "Cloning and characterization of genes responsive to the hepatocarcinogenic peroxisome proliferator Wy-14,643 reveals diverse mechanisms of regulation including activation of a cyclophilin," Proc. Am. Assn. Cancer Res. 35:547 (1994).

8. Sausen, P.J., Rose, M.L., and Cattley, R.C.: "Evaluation of 8-hydroxy-2'-deoxyguanosine levels in rat liver mitochondrial DNA following exposure to the peroxisome proliferator Wy-14,643," Proc. Am. Assn. Cancer Res. 35:155 (1994).

9. Sausen, P., Teets, V., Voss, K., and Cattley, R.: "Subacute effects of gemfibrozil in the rat liver," Toxicologist 14:286 (1994).

10. Cattley, R.C., and Glover, S.E.: "Effect of chronic feeding of peroxisome proliferators on levels of DNA oxidation in rat liver," Proc. Am. Assn. Cancer Res. 34:172. (1993).

11. Miller, R.T., Cattley, R.C., Marsman, D.S., Lyght, O., and Popp, J.A.: "Differential expression of TGFα in liver foci induced by diethylnitrosamine initiation and peroxisome proliferator promotion," Proc. Am. Assn. Cancer Res. 34:150 (1993).

12. Castellino, S., Elion, G.B., Griffith, O.W., Dewhirst, M., Kurtzberg, J., Cattley, R.C., Scott, P., Bigner, D.D., and Friedman, H.S.: "Development and use of a model of Melphalan-induced gastrointestinal toxicity in mice," Proc. Am. Assn. Cancer Res. 33:426 (1992).

13. Cattley, R.C., Murkofsky, R.L., Glover, S.E., and Popp, J.A.: "Effect of WY-14,643 and phenobarbital on hyperplasia and DNA base oxidation in rat liver," Proc. Am. Assn. Cancer Res. 33:189 (1992).

14. Laskowitz, D.T., Elion, G.B., Dewhirst, M.W., Griffith, O.W., Cattley, R.C., Bigner, D.D., and Friedman, H.D.: "Enhancement of melphalan-induced gastrointestinal toxicity in mice treated with regional hyperthermia and BSO-mediated glutathione depletion," Proc. Am. Assn. Cancer Res. 32:390 (1991).

15. Cattley, R.C., Marsman, D.S., and Popp, J.A.: "Effect of age on the carcinogenicity of the peroxisome proliferator WY-14,643 in rats," Proc. Am. Assn. Cancer Res. 31:151 (1990).

16. Popp, J.A., Marsman, D.S., and Cattley, R.C.: "Cell proliferation and promotion in the hepatocarcinogenicity of peroxisome proliferating chemicals," Environ. Mol. Mutagen 14:s15 (1989).

17. Cattley, R.C., Smith-Oliver, T., Butterworth, B.E. and Popp, J.A.: "Quantitation of unscheduled DNA synthesis (UDS) in hepatocytes from rats treated with the peroxisome proliferator WY-14,643 (WY)," Toxicologist 8:104 (1988).

18. Cattley, R.C., and Popp, J.A.: "Differences in the hepatic promotional activities of the peroxisome proliferator WY-14,643 and phenobarbital in rats," Proc. Am. Assn. Cancer Res. 29:165 (1988).

19. Marsman, D.S., Cattley, R.C., and Popp, J.A.: "Contrasting effects of di(2-ethylhexyl)phthalate and WY-14,643 on hepatocyte proliferation and carcinogenicity in male F344 rats," Proc. Am. Assn. Cancer Res. 29:87 (1988).

20. Neptun, D.A., Cattley, R.C., and Popp, J.A.: "Bile acid profiles and serum enzyme alterations in rats fed the hepatocarcinogenic peroxisome proliferator WY-14,643," Clin. Chem. 34:1196 (1988).

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22. Cattley, R.C., and Popp, J.A.: "Effect of the peroxisome proliferator hepatocarcinogen WY-14,643 on foci of altered hepatocytes induced by diethylnitrosamine and phenobarbital in rats," Proc. Am. College Vet. Path., 38th Annual Meeting, pg. 131 (1987).

23. Marsman, D.S., Cattley, R.C., and Popp, J.A.: "Comparative effects of the peroxisome proliferating agents, di(2-ethylhexyl)phthalate (DEHP) and WY-14,643 (WY) in rat liver," Toxicologist 7:165 (1987).

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25. Cattley, R.C., Richardson, K.K., Popp, J.A., and Butterworth, B.E.: "Effects of peroxisome proliferator carcinogens (PPC) on unscheduled DNA synthesis (UDS) in primary rat hepatocytes as monitored by quantitative autoradiography," Proc. Am. Assn. Cancer Res. 27:106 (1986).

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INVITED PRESENTATIONS (since 1990)

December 13, 1995: "Relationship of Cell Proliferation and Promotion to the Carcinogenicity of Peroxisome Proliferators in Rodent Liver," ILSI Meeting, Do Peroxisome Proliferators Pose a Hepatocarcinogenic Hazard to Humans? Arlington, VA.

June 15, 1995: "Preliminary Report: Committee on Nomenclature of Proliferative Lesions of the Mouse Liver," Society of Toxicology Pathologists 14th International Symposium, San Diego, CA.

December 7, 1994: "Mechanism of Hepatic Carcinogenicity by Peroxisome Proliferators," Symposium on Anitoxidants, Oxidants, and Free Radicals, sponsored by the Association of Government Toxicologists, National Capital Chapter of the Society of Toxicology, and the Chesapeake Chapter of Sigma Xi, Bethesda, MD.

November 18, 1994: "Molecular Mechanisms of Carcinogenicity of Peroxisome Proliferators," Department of Medical Nutrition, Novum, Karolinska Institute, Huddinge, Sweden.

November 10, 1994: "Mechanisms and Relevance of Peroxisome Proliferator-Associated Carcinogenesis," Seminar, Department of Pathology, University of North Carolina at Chapel Hill, NC.

October 25, 1994: "The role of peroxisome proliferation in nongenotoxic carcinogenicity", American College of Toxicology: Symposium on Nongenotoxic Carcinogenesis, Williamsburg, VA.

October 23, 1994: "Hepatic metabolism and toxicity in intact animals", ISSX Short Course: Studies on Drug metabolism and Toxicity at Various Levels of Organization in the Liver, Raleigh, NC.

October 21, 1994: "Mechanisms of carcinogenicity by peroxisome proliferators", Genetic Toxicology Association, Philadelphia, PA.

December 3, 1993: "Peroxisome proliferators: potential role of altered hepatocyte growth and differentiation in tumor development", 7th International Conference on Carcinogenesis and risk Assessment, Austin, TX.

August 26, 1993: "Mechanisms of peroxisome proliferator hepatocarcinogenesis", Department of Comparative Medicine, University of Alabama-Birmingham, Birmingham, AL.

November 14, 1992: "Detection of nongenotoxic carcinogens: cell proliferation in liver carcinogenesis", European Science Foundation Research Conference on Mechanisms of Toxicity, San Feliu de Guixols, Spain.

November 9, 1992: "Potential mechanisms of peroxisome proliferator-induced hepatocarcinogenesis in rodents", 4th Mouse Liver Tumor Workshop, ILSI-EPA, Washington, DC.

November 13, 1990: "Comparative morphology of liver tumors", American College of Veterinary Pathologists, Phoenix, AZ.

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EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

MICHAEL R. ELWELL
VETERINARY PATHOLOGIST

EDUCATION (Civilian):
Kansas State University, B.S., Biology, 1970
Kansas State University, D.V.M., 1972
University of Kansas, Ph.D., Pathology, 1982

EDUCATION (Uniformed/Federal Services):
Officer Basic Course, 1972
Veterinary Officers Statistics, 1976
Veterinary Pathology Preceptorship, 1975-1978
Officer Advanced Career Course, 1981-1982
Program Officials Guide to Contracting, 1986
Role of Managers and Supervisors in Employee Development, 1993

BOARD CERTIFICATION:
Veterinary Medicine, National Board, 1972
Veterinary Medicine, Kansas Board, 1972
American College of Veterinary Pathologists, 1978

PRESENT POSITION AND EXPERIENCE:

1995-Present. Director, Virginia Laboratory, Experimental Pathology Laboratories, Inc. (EPL®), Herndon, Virginia 22070.

Responsible for overall management and direction of EPL's Virginia Laboratory. Responsible for the microscopic evaluation of tissues from experimental animals used in a variety of toxicological studies.

1993-1995. Head, Pathology Group, Environmental Toxicology Program, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina 27709

Major Responsibilities: Planned, directed, and coordinated all aspects of the Pathology Group activities relating to pathology and preparation of the NTP technical reports. This included a program to develop and provide current diagnostic pathology criteria, standardization

MICHAEL R. ELWELL, D.V.M., Ph.D. - Continued

PRESENT POSITION AND EXPERIENCE - Continued:

on monitoring animal bioassay testing, determination of pathology diagnoses, and evaluation of final test results for assessment of chemical carcinogenesis. Served on NTP design and review committees to evaluate and interpret results from toxicity and carcinogenicity studies to make recommendations for appropriateness of further testing and study design. Represented the NIEHS and NTP at the national (EPA, FDA, NIH, and CDC) and international (WHO, IARC, and IPCS) levels by serving on scientific review committees. In addition, supervised several scientists and served as co-project officer for two pathology support contracts ($2.5 million each).

1989-1993. Head, Toxicologic Pathology (TPG), Laboratory of Experimental Pathology (LEP), NIEHS, Research Triangle Park, North Carolina.

Major Responsibilities: Supervisor for the NIEHS histology and electron microscopy laboratories (six technicians), two research laboratory technicians, one secretary, and two veterinary pathologists. Contributed to the design and conduct of toxicity studies for independent and collaborative research and participated in the design and development of pathology protocols for the conduct of National Toxicology Program (NTP) toxicity studies. Responsible for the final evaluation and interpretation of pathology results from toxicity studies conducted for the NTP and presented as NTP Toxicity Reports for peer review and publication in the scientific literature.

MICHAEL R. ELWELL, D.V.M., Ph.D. - Continued

PARTICIPATION WITH NATIONAL AND INTERNATIONAL AGENCIES - Continued:

Environmental Protection Agency (EPA):

EPA Dermal Bioassay Workshop, NIEHS, Research Triangle Park, North Carolina, May 18-19, 1988.

EPA Peer Review Workshop on alpha 2 microglobulin: Association with Renal Toxicity and Neoplasia in the Male Rat, Cancer Work Group, Gaithersburg, Maryland, November 13-14, 1990.

National Institutes of Health:

National Institutes of Health, Special Review Section, Division of Research Grants, Review Panel for SBIR, August 2, 1988.

National Institutes of Health, Special Review Section, Division of Research Grants, Review Panel for SBIR, June 21, 1990.

National Institute for Diabetes and Digestive and Kidney Diseases, Review Panel Member for RFP No. NIH-NIDDK 91-5, September 16, 1991.

Center for Disease Control:

Ribavirin for Hantavirus Pulmonary Syndrome and Pancreatitis-Expert Consultant, July 19, 1994, Atlanta, Georgia.

International Agency for Research on Cancer (IARC):

Working Group on the Evaluation of Carcinogenic Risks to Humans - IARC Monograph Volume 47: Organic Solvents, Some Resin Monomers, Some Pigments and Occupational Exposures in Painting Trades, October 18-25, 1988, Lyon, France.

Working Group on the Evaluation of Carcinogenic Risks to Humans - IARC Monograph Volume 60, February 15-22, 1994, Lyon, France.

World Health Organization (WHO):

WHO 34th Joint FAO/WHO Expert Committee on Food Additives, January 30-February 8, 1989, Geneva, Switzerland.

WHO 36th Joint FAO/WHO Expert Committee on Food Additives, February 5-14, 1990, Rome, Italy.

WHO 39th Joint FAO/WHO Expert Committee on Food Additives, February 3-12, 1992, Rome, Italy.

WHO International Program on Chemical Safety, Environmental Health Criteria for Cresols, June 27-July 1, 1994, Carshalton, UK.

MICHAEL R. ELWELL, D.V.M., Ph.D. - Continued:

OTHER PROFESSIONAL ACTIVITIES:

Office of the Surgeon General:
Nomination Board Member for Chief Professional Officer, Dietician Category, United States Public Health Service

American College of Veterinary Pathologists:
Examination Committee Member, 1990, 1992-1995.

Journal of Veterinary Pathology:
Editorial Board

Journal of Environmental Health Perspectives:
Editorial Review Board

Journal of Toxicology and Applied Pharmacology:
Manuscript Reviewer

Society of Toxicologic Pathologists:
Standard Nomenclature and Diagnostic Criteria in Toxicologic Pathology, Subcommittee Member for Heart and Vasculature

NTP Liaison to Society of Toxicologic Pathologists

Council Member

PROFESSIONAL ORGANIZATIONS:

American College of Veterinary Pathologists
Society of Toxicologic Pathologists
American Veterinary Medical Association
Kansas Veterinary Medical Association
Commissioned Officers of America

HONOR SOCIETIES AND FRATERNAL ORGANIZATIONS:

Phi Kappa-Phi
Phi Eta Sigma
Phi Zeta
Beta Theta Pi

MICHAEL R. ELWELL, D.V.M., Ph.D. - Continued:

PUBLICATIONS:

Mechanisms of Oral Staphylococcal Enterotoxin B-Induced Emesis in the Monkey. Elwell, M.R., Lui, C.T., Beisel, W.R., and Spertzel, R.O, Proc. Soc. Exp. Biol., Med., 148:424, 1975.

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Possible Endotoxemia in Rabbits After Intravenous Injection of Staphylococcal Enterotoxin B. Pettit, G.W., Elwell, M.R., and Jahrling, P.B., J. Infect. Dis., 135:646, 1977.

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Chordomas in F344 Rats. Stefanski, S.A., Elwell, M.R., Mitsumori, K., Yoshitomi, K., Dittrich, K., and Giles, H.D., Vet. Pathol., 25:42, 1988.

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Subchronic Toxicity of Orally-Administered Theophylline in F344 Rats and B6C3F1 Mice. Collins, J.J., Elwell, M.R., Lamb, J.C., Manus, A.G., Heath, J.E., and Makovec, T.K., Fund. Appl. Pharmacol., 11:472, 1988.

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MICHAEL R. ELWELL, D.V.M., Ph.D. - Continued

PUBLICATIONS - Continued:

Fibrosarcoma, Dermis and Subcutis, Mouse. Boorman, G.A., Eustis, S.L., and Elwell, M.R., In: Monographs on the Pathology of Laboratory Animals. The Integument and Mammary Glands, Jones, T.C., Mohr, U., Hunt, R.D., eds., Springer-Verlag, Berlin, pp. 95-100, 1989.

Fibroma, Dermis and Subcutis, Mouse. Boorman, G.A., Elwell, M.R., and Eustis, S.L., In: Monographs on the Pathology of Laboratory Animals. The Integument and Mammary Glands, Jones, T.C., Mohr, U., Hunt, R.D., eds., Springer-Verlag, Berlin, pp 93-95, 1989.

Kidney and Urinary Bladder Lesions in F344 Rats and B6C3F1 Mice After 13 Weeks of 2,2-bis(bromomethyl)-1,2-propanediol (BMP). Elwell, M.R., Dunnick, J.K., Brown, H.R., and Montgomery, C.A., Fundam. Appl. Toxicol., 12:480, 1989.

Toxicity Studies of Amphetamine Sulfate, Ampicillin Trihydrate, Codeine, 8-Methoxypsoralin, a-Methyldopa, Penicillin VK, and Propantheline Bromide in Rats and Mice. Dunnick, J.K. and Elwell, M.R., Toxicology, 56:123, 1989.

Lung Toxicity After 13-Week Inhalation Exposure to Nickel Oxide, Nickel Subsulfide, or Nickel Sulfate Hexahydrate in F344/N Rats and B6C3F1 Mice. Dunnick, J.K., Elwell, M.R., Benson, J.M., and Hobbs, C.H., Fundam. Appl. Toxicol., 12:584, 1989.

Epididymal Interstitial (Leydig) Cell Tumors in B6C3F1 Mice. Mitsumori, K., Talley, F.A., and Elwell, M.R., Vet. Pathol., 26:65, 1989.

Subchronic Effects of Exposure to Octachlorodibenzodioxin (OCDD). Birnbaum, L.S., Couture, L.A., and Elwell, M.R., Chemosphere, 18:389, 1989.

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Chapter 20: Neoplasms of the Testes. Boorman, G.A., Eustis, S.L., and Elwell, M.R., In: Atlas of Tumor Pathology of the Fischer Rat, Stinson, Schuller, and Reznik, eds., CRC Press, Florida, pp 409-414, 1989.

MICHAEL R. ELWELL, D.V.M., Ph.D. - Continued

PUBLICATIONS - Continued:

Subchronic Toxicity of Tetrahydrofuran Vapors in Mice and Rats. Chhabra, R.S., Elwell, M.R., Chou, B., Miller, R.A., and Renne, R.A., Fundam. Appl. Toxicol., 14:338, 1990.

Relative Toxicity and Tumor Promoting-Ability of TCDD, PCDF, and HCDF in Hairless Mice. Hebert, C.D., Harris, M.W., Elwell, M.R., and Birnbaum, L.S., Toxicol. Appl. Pharmacol., 102:362, 1990.

Subchronic Toxicology Studies of Hexachloro-1,3-butadiene (HCBD) in B6C3F1 Mice by Dietary Incorporation. Yang, S.H., Abdo, K.M., and Elwell, M.R., J. Environ. Pathology, Toxicology and Oncology, 9:323, 1990.

Toxicity of 4-vinyl-cyclohexene After 13-Week Dermal or Oral Exposure in Rats and Mice. Chhabra, R.S., Elwell, M.R., and Peters, A., Fundam. Appl. Toxicol., 14:745, 1990.

Inhalation Toxicity Studies of Cobalt Sulfate in F344 Rats and B6C3F1 Mice. Bucher, J.R., Elwell, M.R., Thompson, M.B., Chou, B.J., and Renne, R., Fundam. Appl. Toxicol., 15:357, 1990.

Salivary Glands. Neuenschwander, S.B. and Elwell, M.R., Chapter 4 In: Pathology of the Fischer Rat, Boorman, Eustis, Elwell, Montgomery, and MacKenzie, eds., Academic Press, Inc., San Diego, pp. 31-42, 1990.

Small and Large Intestine. Elwell, M.R. and McConnell, E.E., Chapter 5 In: Pathology of the Fischer Rat, Boorman, Eustis, Elwell, Montgomery, and MacKenzie, eds., Academic Press, Inc., San Diego, pp. 43-61, 1990.

Skin and Subcutis. Elwell, M.R., Stedham, M.A., and Kovatch, R.M., Chapter 17 In: Pathology of the Fischer Rat, Boorman, Eustis, Elwell, Montgomery, and MacKenzie, eds., Academic Press, Inc., San Diego, pp. 261, 1990.

Spleen, Lymph Nodes, and Thymus. Stefanski, S.A., Elwell, M.R., and Stromberg, P.C., Chapter 22 In: Pathology of the Fischer Rat, Boorman, Eustis, Elwell, Montgomery, and MacKenzie, eds., Academic Press, Inc. San Diego, pp. 369-393, 1990.

Male Accessory Sex Glands, Penis and Scrotum. Boorman, G.A., Elwell, M.R., and Mitsumori, K., Chapter 25 In: Pathology of the Fischer Rat, Boorman, Eustis, Elwell, Montgomery, and MacKenzie, eds., Academic Press, Inc. San Diego, pp. 419-428, 1990.

PUBLICATIONS - Continued:

Toxicity and Carcinogenicity Studies of Hydrochlorothiazide in F344 Rats and B6C3F1 Mice. Bucher, J.R., Huff, J.E., Haseman, J.K., Eustis, S.L., and Elwell, M.R., J. Appl. Toxicol., 15:359, 1990.

Tumours of the Harderian Gland. Elwell, M.R. and Boorman, G.A., In: Pathology of Tumours in Laboratory Animals, Tumours of the Rat, Vol. 1, Turusov V., ed., IARC Scientific Publications, pp 79-88, 1990.

Tumours of the Salivary and Lacrimal Glands. Elwell, M.R. and Leininger, J., In: Pathology of Tumours in Laboratory Animals, Tumours of the Rat, Vol. 1, Turusov V., ed., IARC Scientific Publications, pp 89-108, 1990.

Comparative Toxicity Studies of Ethylene Dichloride in Three Rat Strains and B6C3F1 Mice: Administration in the Drinking Water and By Gavage. Morgan, D.L., Bucher, J.R., Elwell, M.R., Lilja, H.S., and Murthy, A.S.K., Fd. Chem. Toxic., 28:839, 1990.

Toxicity of p-chloroaniline in Rats and Mice. Chhabra, R.S., Thompson, M.B., Elwell, M.R., and Gerken, D.K., Fd. Chem. Toxic. 28(10):717, 1990.

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Comparative Toxicity and Tissue Distribution of Antimony Potassium Tartrate in Rats and Mice Dosed by Drinking Water or Intraperitoneal Injection. Dieter, M.P., Jameson, C.W., Elwell, M.R., Lodge, J.W., Hejtmancik, M., Grumbein, S.L., Ryan, M., and Peters, A.C., J. Toxicol. Env. Health, 34:51, 1991.

Chordoma, Rat. Elwell, M.R., Stefanski, S., and Mitsumori, K., In: The Cardiovascular and Musculoskeletal Systems, Monographs on Pathology of Laboratory Animals, Jones, T.C., Mohr, U., and Hunt, R.D., eds., Springer-Verlag, Berlin, pp 214-218, 1991.

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MICHAEL R. ELWELL, D.V.M., Ph.D. - Continued

PUBLICATIONS - Continued:

Subchronic Toxicity Studies of Dietary Phenolpthtalein in F344 Rats and B6C3F1 Mice. Dietz, D.D., Elwell, M.R., Shelby, M.D., Thompson, M.B., Chapin, R.E., Filler, R., and Stedham, M.A., Fundam. Appl. Toxicol. 18:48, 1992.

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MICHAEL R. ELWELL, D.V.M., Ph.D. - Continued

PUBLICATIONS - Continued:

Toxicity Studies of Cupric Sulfate Administered in Drinking Water and Feed to F344.N Rats and B6C3F1 Mice. Hebert, C.D., Elwell, M.R., Travlos, G.S., Fitz, C.J., and Bucher, J.R., Fundam. Appl. Toxicol., 21:461, 1993.

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PRESENTATIONS:

Mechanisms of Oral Staphylococcal Enterotoxin B-Induced Emesis in the Monkey. 53rd Annual Meeting of Federation of American Societies for Experimental Biology, Atlantic City, New Jersey, April 7-12, 1974.

Changes in Blood pH in Rats After Infection with Streptococcus Pneumoniae. United States Army Medical Research Institute for Infectious Diseases Ad Hoc Committee Seminar USAMRIID, Frederick, Maryland, March 1975.

Immunity of Toxoplasmosis in Hamsters. 25th SEAMO-TROPMED Seminar, Immunology of Tropical Parasitic Infections in Asia and Pacific Region, The Institute for Medical Research, Kuala Lampur, Malaysia, October 19-21, 1982.

The Pathogenesis of Toxoplasmosis and the Development of Protective Immunity in Hamsters. FAO/SIDA Follow-Up Seminar on Veterinary Pathology, Nakhom Pathom, Thailand, February 14 - March 4, 1983.

Doxycycline Prophylaxis for Leptospirosis in Hamsters and Monkeys. Annual Meeting of the American Society of Tropical Medicine and Hygiene, San Antonio, Texas, December 1983.

Comparison of Findings in Short-Term Toxicity and Long-Term Carcinogenicity Studies. The Reproductive System of Laboratory Animals - A Histopathology Seminar, ILSI, Harvard Medical School, Boston, Massachusetts, June 16-18, 1987.

Primary Cardiac Neoplasms in the F344 Rat. Annual Meeting of American College of Veterinary Pathologists, Monterey, California, November 11, 1987.

MICHAEL R. ELWELL, D.V.M., Ph.D. - Continued

PRESENTATIONS - Continued:

Biological Considerations in Carcinogenicity Studies. National Capital Area Chapter of the Society of Toxicology, Washington, D.C., November 17, 1987.

Toxicity of 4-chloro, a,a,a-trifluorotoluene. Annual Meeting of the American College of Veterinary Pathologists (poster), Phoenix, Arizona, December 11, 1990.

Prechronic Toxicity as a Predictor of Carcinogenicity - Preneoplastic Lesions. Third Japan-United States Joint Meeting on the Toxicological Characterization of Environmental Chemicals, Kona, Hawaii, February 4-6, 1991.

Carcinogenicity of Trihalomethanes in Rodents - Morphology and Biology of Intestinal Tumors in F344 Rats. Workshop on Trihalomethanes and Other Environmental Factors That Contribute to Colorectal Cancer, NIEHS, Research Triangle Park, North Carolina, September 14, 1993.

ABSTRACTS:

Mechanisms of SEB-Induced Emesis in the Monkey. Elwell, M.R., Liu, C.T., Spertzel, R.O., Beisel, W.R., and Overman, R.R., Federation Proceedings, 33(3):362, 1974.

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Spontaneous and Induced Non-neoplastic Vascular Lesions in F344 Rats. McDonald, M.M., Elwell, M.R., and Leininger, J., Annual Meeting of the American College of Veterinary Pathologists (poster), Kansas City, Kansas, November 1, 1988.

Structural Alerts for Leukemia: The Alkyl Phosphonic Ester (APE) Structure. Dieter, M.P., Jameson, C.W., Elwell, M.R., The Toxicologist, 1989.

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Renal Toxicity of P-nitrobenzoic Acid in 13-Week and 2-Year Feed Studies in F344 Rats. Sills, R., Dunnick, J., Hailey, R., and Elwell, M., American College of Veterinary Pathologists, 1993.

MICHAEL R. ELWELL, D.V.M., Ph.D. - Continued:

ABSTRACTS - Continued:

Influence of Dietary Fat and Fiber on Growth and Tumor Incidences in F344 Rats. Rao, G.N., Edmondson, J., and Elwell, M.R., Society of Toxicologic Pathologists, The Toxicologist, 14(1):1175, 1994.

Toxicity of Sodium Selenate and Sodium Selenite Given to Rats and Mice in Their Drinking Water for 13 Weeks. Abdo, D.M., Bucher, J.R., Elwell, M.R., and Travlos, G.S., Experimental Biology, 1994.

Comparative Carcinogenicity of Selected Chemicals With or Without Perinatal Exposure in Rats and Mice. Chhabra, R.S., Bucher, J.R., Haseman, J.K., and Elwell, M.R., XVI International Cancer Congress, New Delhi, India, 1994.

Colorectal Cancer in Rats and Mice After Administration of Brominated Chemicals. Dunnick, J.K. and Elwell, M.R., XVI International Cancer Congress, New Delhi, India, 1994.

U.S. National Toxicology Program (NTP) Studies on Glycol Ethers. Bucher, J., Dieter, M., Roycroft, J., Elwell, M., and Chapin, R., International Symposium on Health Hazards of Glycol Ethers, 1994.

CURRICULUM VITAE

Joel R. Leininger, D.V.M., Ph.D.

2-96

Social Security No. 508-62-0460
Date of Birth: January 20, 1948
Place of Birth: Lincoln, Nebraska, USA
Family Status: Married (Patricia M. Turlington); Children:Andrew G., (1-30-79); Peter R., (8-28-82); Jeffrey J., (4-13-88)

EDUCATION:

High School Diploma, Columbus, Nebraska, 1966
D.V.M., Iowa State University, Ames, IA, 1972
Residency in Comparative Pathology, University of California Veterinary Medical Teaching Hospital, Davis, CA, 1972-1973
Ph.D., Pathology, University of Georgia, Athens, GA, 1976

CONTINUING EDUCATION COURSES:

Drug and Biologic Safety Evaluation, The Institute for Applied Pharmceutical Sciences, The Center for Professional Advancement, East Brunswick, NJ, July 27-29, 1992.

Concepts in Molecular Biology, American Society for Investigative Pathology, Bethesda, MD, October 28-31, 1993

PROFESSIONAL LICENSURE AND CERTIFICATION (by examination):

Iowa, Nebraska, Minnesota, and California Veterinary Licenses
Diplomate, American College of Veterinary Pathologists (1977)

EXPERIENCE:

1995-present	Senior Pathologist, Integrated Laboratory Systems, Research Triangle Park, NC. Resposible for technical aspects of necropsy, histology, and histopathology laboratories and for overall pathology support for contracts involving molecular mechanisms of chemical carcinogenesis.
1993-1995	Visiting Scientist, Experimental Pathology and Toxicology Department, Chemical Industry Institute of Toxicology, Research Triangle Park, NC. Mechanistic studies involving chlorine and formaldehyde rodent bioassays, and the rodent nasal lesions following chloroform exposure.
1990-1993	Division Director, Pathology Associates, Inc. (PAI), Research Triangle Park, NC. Responsible for all operations of the laboratory, including electron microscopy, histology, quality assurance, histopathology, and personnel management and staffing. Served as pathologist, on contractual basis, for several pharmaceutical companies in their drug discovery and develpment programs. Histopathology safety assessment-type duties primarily concerned National Toxicology Program Pathology Working Groups. Served as Chair for approximately 20 Pathology Working Groups.

1987-1990	Staff Pathologist, National Toxicology Program (NTP), NIH, Research Triangle Park, NC. Duties included participating on Pathology Working Groups, reviewing contract laboratory proposals, writing and reviewing pathology aspects of Technical Reports, and serving as liaison pathologist to contract laboratories.
1980-1987	Associate Professor (with tenure), Department of Veterinary Pathobiology, College of Veterinary Medicine, University of Minnesota, St. Paul, MN. Coordinator of systemic pathology course in professional curriculum. Responsible for urinary system portion of systemic pathology course and for portion of graduate oncology course. Coordinator of University of Minnesota Veterinary Medical Teaching Hospital surgical pathology laboratory and served on necropsy team as one of the teaching pathologists.
1976-1980	Assistant Professor, Department of Preventive Medicine and Environmental Health, College of Medicine, University of Iowa, Iowa City, IA. Collaborated on interdisciplinary environmental health research projects and provided laboratory animal diagnostic service on university-wide basis. Responsible for academic course in comparative pathology (Animal Models of Human Diseases). Responsible for basic pathology portion of introductory health science course for graduate students.
1973-1976	Veterinary Medical Resident/Ph.D. program, University of Georgia, Athens, GA. Thesis research on effect of zirconium and aluminum compounds on respiratory system. Advisor: R.L. Farrell.
1972-1973	Resident in Pathology, University of California, Davis, CA. Necropsy, biopsy, and senior student teaching services of the pathology department. Participated in weekly seminars.
Summer 1971	Assistant in mixed veterinary practice. C.L. Stoehr, D.V.M., Plattsmouth, NE.
Summer 1970	Diagnostic Laboratory Assistant, Dellen, Inc., Omaha, NE

PROFESSIONAL AFFILIATIONS:

American College of Veterinary Pathologists (ACVP), Diplomate in Pathology
Society of Toxicologic Pathologists (STP), Full Member

SERVICE TO PROFESSIONAL ORGANIZATIONS:

Vice-Chair and Chair, Renal Pathology Specialty Group-ACVP
Vice-Chair and Chair, Bone and Joint Pathology Specialty Group-ACVP
Member, Coordinating Committee for Standardized Pathology Nomenclature and Diagnostic Criteria-STP
Member, Subcommittee for Standardized Pathology Nomenclature and Diagnostic Criteria for Proliferative and Nonproliferative lesions of Bone and Joints in Rats and Mice-STP

AWARDS AND HONORARIES:

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AREAS OF INTEREST

Morphology and mechanisms of bone, renal, nasal, upper gastointestinal tract, liver, and pulmonary lesions; general toxicologic pathology

UNIVERSITY AND DEPARTMENTAL COMMITTEES:

University of Iowa Animal Care Committee, 1977-1980; Chairman, 1979-1980

Department of Preventive Medicine, University of Iowa, Admissions and Standards Committee, 1978-1980

College of Veterinary Medicine, University of Minnesota, Animal Care Committee, 1980-1985; Chairman, 1980-1981, 1983-1984

College of Veterinary Medicine, University of Minnesota, Curriculum Committee, 1985-1986, 1986-1987

GRADUATE STUDENTS ADVISED AND GRADUATE COMMITTEES:

John Abraham, Ph.D., Examination Committee, University of Iowa
Paul Liu, Ph.D., Examination Committee, University of Iowa
Shehu Abdullahi, Ph.D., Examination Committee, University of Minnesota
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Alan L. Metz, Ph.D., Advisory and Examination Committee, University of Minnesota
John A. Opuda, Ph.D., Examination Committee, University of Minnesota
Joseph S. Haynes, Ph.D., Advisory and Examination Committees, University of Minnesota
Tsang-Long Lin, Ph.D., Major Advisor, University of Minnesota
Laurence O. Whiteley, Ph.D., Major Advisor (to 1987), University of Minnesota

PUBLICATIONS:

Leininger, J.R., Monticello, T.M., Gross, E.A., Morgan, K.T. (1996). Morphogenesis of formaldehyde-Induced nasal carcinomas in male F344 rats. Fund. Appl. Toxicol. In preparation.

Monticello, T.M., Swenberg, J.A., Gross, E.A., Leininger, J.R., Kimbell, J.S., Seilkop, S., Starr, T.B., Gibson, J.E., Morgan, K.T. (1996). Correlation of regional and nonlinear formaldehyde-induced nasal cancer with proliferating populations of cells. Cancer Res. In press (April, 1996).

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Leininger, J.R., Herbert, R.A., Morgan, K.T. (1996). Aging changes in the upper respiratory tract. In Pathobiology of the Aging Mouse. (U. Mohr, D. Dungworth, C. Capen, Eds). International Life Sciences Institute/ILSI Press, Washington, DC, In press (June '96).

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Dietz, D.D., Leininger, J.R., Rauckman, E.J., Thompson, M.B., Chapin, R.E., Morrissey, R.L., Levine, B.S. (1991). Toxicity studies of acetone administered in the drinking water of rodents. Fund. Appl. Toxicol. 17(2), 347-360.

Harris, C.L., Klausner, J.S., Caywood, D.D., Leininger, J.R. (1991). Hypercalcemia in a dog with thymoma. J. Amer. Ani. Hosp. Assoc. 27(3), 281-284.

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Leininger, J.R., McDonald, M.M., Abbott, D.P. (1990). Hepatocytes in the mouse stomach. Toxicologic Pathol. 18(4, part 2), 678-686.

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Penaredondo, M.V., Maheswaran, S.K., Whiteley, L., Ames, T.R., Leininger, J.R. (1988). Production and partial characterization of monoclonal antibodies to pasteurella hemolytica A1 capsular polysaccharide and lipopolysacharide. Amer. J. Vet. Res. 49, 1962-1968.

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Vega, M.V., Maheswaran, S.K., Leininger, J.R., Ames, T.R. (1987). Adaptation of a colorimetric microtiter assay for quantifying pasteurella hemolytica A1 leucotoxin and antileukotoxin. Amer. J. Vet. Res. 48, 1559-1564.

Bailie, N.C., Osborne, C.A., Leininger, J.R., Fletcher, T.F., Johnston, S.D., Ogburn, P.N., Griffith, D.P. (1986). Teratogenic effect of acetohydroxamic acid in clinically normal beagles. Amer. J. Vet. Res. 47(12), 2604-2611.

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PRESENTATIONS:

Leininger, J.R. Spontaneous Bone Lesions in Rats and Mice. Invited Speaker. ACVP, December 7, 1993, San Antonio, TX.

Leininger, J.R., Goad, M.E.P., Frantz, J.D. Metaphyseal atrophy in rats from 13-week toxicity studies. ACVP, November 2, 1989, Baltimore, MD.

McDonald, M.M., Leininger, J.R. Hepatocytes in the glandular stomach of B6C3F1 mice. ACVP, November 2, 1989, Baltimore, MD.

Dietz, D.D., Leininger, J.R., Thompson, M.B., Mulligan, L.T., Morrissey, R.L., Levine, B.S. Prechronic toxicity studies of acetone administered in the drinking water of rodents. Society of Toxicology, February 27-March 3, 1989, Atlanta, GA.

Uraih, L.C., Leininger, J.R., Eustis, S.L., Horton, S., Maronpot, R.R. Immunocytochemical characterization of uterine mesenchymal tumors in F344 rats. ACVP, November 2, 1988, Kansas City, MO.

Leininger, J.R., Irwin, R., Elwell, M.R., Jokinen, M.P., Mezza, L. Renal lesions due to 90 day exposure to benzonitrile. ACVP, November 2, 1988, Kansas City, MO.
McDonald, M.M., Elwell, M.R., Leininger, J.R. Spontaneous and induced non-neoplastic vascular lesions in F344 rats. ACVP, November 1, 1988, Kansas City, MO.

Tipton, C.M., McMahon, S., Pauli, E.L., Leininger, J.R., Lauber, C. Response of adult stroke-prone hypertensive rats (SP-SHR) to moderate exercise training. American College of Sports Medicine Meeting, 1987.

Townsend, E.L., Maheswaran, S.K., Leininger, J.R., Ames, T.R. Detection of antibody to pasteurella hemolytica capsular polysaccharide with an enzyme-linked immunosorbent assay. CRWAD, November 11, 1985, Chicago, IL.

Vega, M., Meheswaran, S.K., Ames, T.R., Leininger, J.R. Adaption of a colorimetric assay for quantifying pasteurella hemolytica leukotoxin and antileukotoxin. CRWAD, November 11, 1985, Chicago, IL.

Lin, T.-L., Bey, R.F., Leininger, J.R. Comparative immunopathology of experimentally-induced leptospirosis in hamsters.- American Society for Microbiology, March 1984, St. Louis, MO.

Maheswaran, S.K., Leininger, J.R., Ames, T.R., Townsend, E.L. Immune response to pasteurella hemolytica leukotoxin. CRWAD, November 12, 1984, Chicago, IL.

Opuda-Asibo, J., Townsend, E.L., Maheswaran, S.K., Leininger, J.R. Immunological defense mechanisms against pasteurella hemolytica in the bovine lung. Symposium on Bovine Respiratory Disease, September 1983, Amarillo, TX.

Leininger, J.R., Polzin, D.J. Glomerular lesions in dogs with reduced renal mass. ACVP, November 30, 1983, San Antonio, TX.

Ames, T.R., Markham, R.J.F., Maheswaran, S.K., Leininger, J.R. Pulmonary response to intratracheal challenge with pasteurella. CRWAD, November 14, 1983, Chicago, IL.

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Tipton, C.M., Matthes, R.D., Leininger, J.R., Sturek, M. Effect of voluntary exercise by stroke-prone SHR groups on select physiological responses. American Physiological Society Meeting, August 20, 1983 (Abstract in the Physiologist).

Leininger, J.R., Donham, K.J., Rubino, M.J., Meyers, W.M. Naturally acquired leprosy in a chimpanzee. Necropsy findings and experimental transmission to other animals. International Academy of Pathology Meeting, February 25, 1980, New Orleans, LA (Abstract in Laboratory Investigation 42:132, 1980).

Massanari, R.W., Wilson, M.L., Leininger, J.R. Susceptibility of in-bred hamster strains to a hamster adopted subacute sclerosing panencephalitis virus (HBS). International Symposium of Canadian Society for Immunology: Genetic Control of Natural Resources to Infection and Malignancy, March 18-20, 1980, Montreal, Canada (Published Proceedings).

Massanari, R.M., Leininger, J.R. Transient atrophy of the thymus gland during influenza A infection. American Society of Microbiology, May, 1980, Miami, FL.

Leininger, J.R., Donham, K.J., Rubino, M.J., Meyers, W.M. Poster display: Spontaneous leprosy in a chimpanzee. XI International Leprosy Congress, November 13-18, 1978, Mexico City, Mexico (Abstract in Int. J. Leprosy 47(2) Suppl.:342-343, 1979).

Donham, K.J., Leininger, J.R., Rubino, M.J. Poster display: Spontaneous leprosy in a chimpanzee. Symposium on Comparative Pathology of Zoo Animals, October 2-4, 1978.

Leininger, J.R., Donham, K.J., and Rubino, M.J. Spontaneous leprosy in a chimpanzee. American Association for Laboratory Animal Science Annual Scientific Session, September 27, 1978, New York, NY.

Leininger, J.R. Some spontaneous diseases of animals. National Society for Histotechnology's 2nd Annual Regional 15 Conference on Histopathologic Techniques, March 30, 1978, Iowa City, IA.

Leininger, J.R. Leprosy in a chimpanzee. Comparative Pathology Course, May 10, 1977, Armed Forces Institute of Pathology, Washington, DC.

Leininger, J.R., Donham, K.J. Spontaneous leprosy-like disease in a chimpanzee. American College of Veterinary Pathologists, Clinical Pathology Specialty Group, December 3, 1976, Miami Beach, FL.

Donham, K.J., Leininger, J.R., Rubino, M.J., Kirchheimer, W. Preliminary report of a leprosy-like disease in a chimpanzee. 18th Annual Midwest Interprofessional Seminar on Disease Common to Animals and Man, September 21-22, 1976, Columbia, MO.

Leininger, J.R., Farrell, R.L. Effect of zirconium and aluminum compounds on the morphology of tracheal organ cultures. Zirconium and Aluminum Toxicity Symposium, July 28-29, 1976, Cincinnati, OH.

Farrell, R.L., Leininger, J.R. Pulmonary reactions of hamster lungs following intratracheal instillation of zirconium and aluminum compounds. Zirconium and Aluminum Toxicity Symposium, July 28-29, 1976, Cincinnati, OH.

Leininger, J.R. Granular cell myoblastoma. 4th Annual Meeting of Southeast Veterinary Pathologists, May 9, 1976, Tifton, GA.

Malone, J.B., Leininger, J.R., Thompson, P.E., Chapman, W.L. Brugia pahangi in golden hamsters: Susceptibility and pathology. Third International Congress of Parasitology 2:632-633 (Proceedings), 1974, Munich, Germany.

Malone, J.B., Leininger, J.R., Thompson, P.E., Chapman, W.L. Golden hamsters as experimental models in filariasis studies. 28th Annual Meeting of Animal Disease Research Workers in Southern States, March 22, 1974, Baton Rouge, LA.

Crowell, W.A., Leininger, J.R. Fine structure of glomeruli in normal cats and cats with selected diseases. 28th Annual Meeting of Animal Disease Research Workers in Southern States, March 22, 1974, Baton Rouge, LA.

Leininger, J.R. A case of bovine hydranencephaly and porencephaly. 2nd Annual Meeting of Southeast Veterinary Pathologists, June 1974, Tifton, GA.

Leininger, J.R., Crowell, W.A. Morphology of autolysed and diseased feline glomeruli. 55th Conference of Research Workers in Animal Diseases, December 3, 1974, Chicago, IL.
Crowell, W.A., Leininger, J.R. Fine structure of glomeruli from autolytic feline kidneys. Southeast Electron Microscopy Society Annual Meeting, May 17, 1974, Chapel Hill, NC.

1 January 1994

CURRICULUM VITAE

Name: Ernest E. McConnell, DVM, MS (Path)
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Date & Place of Birth: November 14, 1937
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Citizenship: United States

Education:

1955 - 1957 - Preveterinary Medicine, The Ohio State University
1957 - 1961 - D.V.M., The Ohio State University
1964 - 1966 - M.S., Department of Pathology, Michigan State University
1965 - 1967 - Resident, Veterinary Pathology Division, Armed Forces Institute of Pathology, Washington, DC

Board Certification:

Diplomate, American College of Veterinary Pathologists, 1968
Diplomate, American Board of Toxicology, 1980

Brief Chronology of Employment:

Jun 1961 - Aug 1961	Small Animal Practitioner, Becker Small Animal Hospital, Columbus, OH
Aug 1961 - Aug 1961	First Lieutenant, U.S. Air Force, Gunter AFB, Montgomery, Al
Oct 1961 - Sep 1964	Base Veterinarian, Hill Air Force Base, Ogden, UT
Sep 1964 - Sep 1965	Graduate Student, Department of Pathology, Michigan State University, East Lansing, MI
Sep 1965 - Oct 1967	Resident, Veterinary Pathology Division, Armed Forces Institute of Pathology, Washington, DC
Oct 1967 - May 1969	Veterinary Pathologist, Aerospace Pathology Branch, Armed Forces Institute of Pathology, Washington, DC
May 1969 - Aug 1972	Veterinary Pathologist, Geographic Pathology Division, Armed Forces Institute of Pathology, Washington, DC with duty in the Pathology Department, Veterinary Research Institute, Onderstepoort, Republic of South Africa
Aug 1972 - Aug 1974	Chief, Pathology Branch, Toxic Hazards Div., 6570 Aerospace Medical Research Lab., Wright-Patterson AFB, OH

Aug 1974 - Nov 1978 Veterinary Pathologist (Grade 05), U.S. Public Health Service, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, NC., Research Pathologist and Head, Comparative Pathology, Chemistry Branch.

Nov 1978 - Jan 1984 Veterinary Director (Grade 06), NIEHS, Chief, Chemical Pathology Branch, Toxicology Research and Testing Program, Research Triangle Park, NC

Sep 1983 - Jan 1985 Veterinary Director (Grade 06). NIEHS, Acting Director, Toxicology Research and Testing Program, Research Triangle Park, NC

Jan 1985 - Oct 1988 Veterinary Director (Grade 06). NIEHS, Director, Division of Toxicology Research and Testing Program, Research Triangle Park, NC

Oct 1988 - present Consultant in Toxicology and Pathology, 3028 Ethan Lane, Raleigh, NC

Military Service:

Aug 1961 - Aug 1974: U.S. Air Force
Aug 1974 - Oct 1988: U.S. Public Health Service

Current Society Memberships:

American Veterinary Medical Association
American College of Veterinary Pathologists
American Board of Toxicology
American Registry of Pathology, AFIP
Commissioned Officers Association, U.S. Public Health Service
North Carolina Chapter of the Society of Toxicology
Society of Toxicology
Society of Toxicologic Pathologists
Charter Member, Alumni Society, Armed Forces Inst. of Pathology

Honors & Special Scientific Recognition:

Distinguished Citizens Award, Hill AFB, Utah, 1964
National Defense Service Medal, 1967
U.S. Air Force Meritorious Service Medal, Wright-Patterson AFB, Ohio, 1974
Adjunct Associate Professor, School of Veterinary Medicine, North Carolina State University, 1978 to present
U.S. Public Health Service Commendation Medal, NIH, Washington, DC, 1978
Study Section-Agent Orange, Veterans Administration, June 1982
Chairman, Natural Exposure Study of Animals in Environmental Health Research Workshop, National Research Council, National Academy of Sciences, April 1985
U.S. Public Health Outstanding Service Medal, NIH, Washington, DC, 1985
Panelist-Speaker, Conference on the Implications of the Bhopal Tragedy, The Workers Policy Project, Newark, New Jersey, March 1985
Task Force Leader, Study of Chemical Tracking Agent (NPPD) used by the Soviet KGB, Moscow, 1985
Panel Member, IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans - Some Chemicals Used in Plastics and Elastomers, Lyon, France, June 1985
Study Director for the NTP Methyl Isocyanate Study, 1985
Board Member, American Board of Toxicology, 1985-1989
Panel Member, Refractory Ceramic Fiber Animal Studies, TIMA, 1986

Panel Member, IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans - Silica and Some Silicates, Lyon, France, June 1986

President, American Board of Toxicology, 1987-1988

Panel Member, Health Consequences of Occupational Exposure to Man-Made Mineral Fibers, TIMA, London, England, January 1987

Panel Member, IARC Working Group to update IARC Monographs: Chemicals and Industrial Processes Associated with Cancer in Humans, Lyon, France, March 1987

Vice Chairman, IARC Working Group on Man-Made Mineral Fibers and Radon, Lyon, France, June, 1987

Panel Member/Rapporateur, IPCS/MARC Task Group Meeting on Man-Made Mineral Fibers, London, England, September 1987

Distinguished Alumnus, College of Veterinary Medicine, The Ohio State University, June, 1988

Panel Member, National Research Council, Board on Environmental Studies and Toxicology, Subcommittee on "Animals as Monitors of Environmental Hazards", 1987-1989

Co-Chairman, Review of EPA Cancer Assessment Guidelines, 1988-1989

Member, National Research Council, Board on Environmental Studies on Toxicology, 1989-1991

Consultant, SAB (Drinking Water Committee and Environmental Health Committee, Environmental Protection Agency, 1988-

Lecturer, Brookings Institute, 1989

Panel Member (ad hoc), EPA-FIFRA Scientific Advisory Panel, 1989

Panel Member/Rapporateur,IPCS/MARK Task Group Meeting on Benzene, Hannover, Germany, December, 1991.

Panel Member, EPA-FIFRA Scientific Advisory Panel, 1992-

FDA Group Recognition Award, Nitrofuran Hearing Team, 1992.

Panel Member, IPCS Task Group Meeting on Synthetic Organic Fibers, London, England, September, 1992.

Panel Member, WHO European Programme for Occupational Health, "Validity of Methods for Assessing the Carcinogenicity of Man-Made Fibers", Copenhagen, Denmark, 1992

Member, Committee on Toxicology, National Research Council, Board on Environmental Studies on Toxicology, 1991-

Chairman, EPA-FIFRA Scientific Advisory Panel, 1993-

Member, EPA Science Advisory Board Executive Committee, 1993-

Editorial Boards:

Medical Research Council of Canada, 1982
Environmental Health Perspectives, 1983
Drug and Chemical Toxicology, 1986
Fundamental and Applied Toxicology, 1989

Papers Published:

1. McConnell, E.E.: Case for diagnosis. Yaba monkey virus. Military Medicine 132:838, 869, 1967.

2. McConnell, E.E.: Garner, F.M. and Kirk, J.H.: Hartmanellosis in a bull. Pathologia Veterinaria 5:1-6, 1968.

3. McConnell, E.E., Cashell, I.G. and Garner, F.M.: Visceral leishmaniasis with ocular involvement in a dog. JAVMA 156:197-203, 1970.

4. McConnell, E.E., Van Rensburg, I.B.J. and Van Wyk, J.A.: A case of adenocarcinoma of the olfactory mucosa of a sheep of possible infectious origin. J.S. African Vet. Med. Assoc. 41:9-12, 1970.

5. Van Rensburg, I.B.J., Roos, C.J. and McConnell, E.E.: Diverticulosis in a cow. J.S. African Vet. Med. Assoc. 41:76, 1970.

6. Bosman, P.P., McConnell, E.E. and Schutte, A.P.: Bovine abortion caused by Aspergillus sp. J.S. African Vet. Med. Assoc. 41:134, 1970.

7. McConnell, E.E. and Tustin, R.C.: Pancreatic calculi in a cow. J.S. African Vet. Med. Assoc. 41:352, 1970.

8. McConnell, E.E., DeVos, A.J., Basson, P.A. and deVos, V.: Isopora papionis n. sp. (Eimeriidae) of the Chacma baboon Papio ursinus (Kerr, 1972). J. Protozool. 18:28-32, 1971.

9. McConnell, E.E., Van Rensburg, I.B.J. and Minne, J.A.: A rapid test for the diagnosis of strychnine poisoning. J.S. African Vet. Med. Assoc. 42:81-84, 1971.

10. McConnell, E.E.: Foot and mouth disease in South Africa - Report of the 1969 outbreak. AF Med. Serv. Digest 22:29-34, 1971.

11. McConnell, E.E., Smit, J.D. and Venter, H.J.: Melanoma in the larynx of a dog. J.S. African Vet. Med. Assoc. 42:189-191, 1971.

12. Schutte, A.P., McConnell, E.E. and Bosman, P.P.: Vibrionic abortion in ewes in South Africa: Preliminary report. J.S. African Vet. Med. Assoc. 42(3):223-226, 1971.

13. McConnell, E.E., Basson P.A. and Pinaar, J.G.: Pneumocystosis in a domestic goat. Onderstepoort J. Vet. Res. 38(2):117-126, 1971.

14. Coffee, G.M., Van Aswegen, P.I.M., McConnell, E.E. and Basson, P.A.: Description of a new nasal mite (Acarina: Halorachnidae) and a new record from the Chacma baboon. Zeitschrift Fur Angewandte Zoologie 58(2):185-190, 1971.

15. McConnell, E.E., Basson, P.A. and deVos, V.: Nasal acariasis in the Chacma baboon (Papio ursinus, Kerr, 1972). Onderstepoort J. Vet. Res. 38:207-214, 1971.

16. Coffee, G.M. and McConnell, E.E.: Pneumonyssus vocalis n. sp. (Acarina: Halarachnidae) a new mite from the laryngeal ventricles of the Chacma baboon (Papio ursinus, Kerr). Zeitschrift Fur angewandte Zoologie 58:265-270, 1971.

17. Bartsch, R.C., Wessells, B.C. and McConnell, E.E.: Myocardial tuberculoma in a Chacma baboon (Papio ursinus, Kerr, 1972). Lab Animals 6:41-47, 1972.

18. McConnell, E.E., Basson, P.A. and deVos, V.: Laryngeal acariasis in the Chacma baboon. JAVMA 161: 678-682, 1972.

19. McConnell, E.E., Tustin, R.C. and deVos, V.: Anthrax in an African buffalo (Syncerus caffer) in the Kruger National Park. J.S. African. Vet. Med. Assoc. 43:181-187, 1972.

20. McConnell, E.E., Basson, P.A., Thomas, S.E. and deVos, V.: Oocysts of Isospora Papionis in the skeletal muscles of chacma baboons. Onderstepoort J. Vet. Res. 39:113-116, 1972.

21. McConnell, E.E., Basson, P.A., Wolstenholme, B., deVos, V. and Malherbe, H.: toxiplasmosis in "free-ranging" Chacma baboons (Papio ursinus) from the Kruger National Park. Trans. R. Soc. Trop. Med. Hyg. 67:851-855, 1973.

22. deVos, V., van Kiekert, C.A.W.J. and McConnell, E.E.: A survey of selected bacteriological infections of the Chacma baboon (Papio ursinus) from the Kruger National Park. Koedoe 16:1-10, 1973.

23. McConnell, E.E.: Lesions found in animals exposed to coal tar aerosols. Proceedings of 4th Annual Conference on Environmental Toxicology. (AMRL-TR-73-125):189-198, 1973.

24. McConnell, E.E., Basson, P.A., deVos, V., Myers, B.J. and Kuntz, R.E.: A survey of diseases among 100 free-ranging baboons (Papio ursinus) from the Kruger National Park. Onderstepoort J. Vet. Res. 41:97-168, 1974.

25. MacEwen, J.D., McConnell, E.E. and Back, K.C.: The effects of 6-month chronic low level inhalation exposures to hydrazine on animals. Proceedings 5th Annual Conference on Environmental Toxicology. AMRL-TR-74-125:225-235, 1974.

26. Harris, A.M., Horton, M.L., Letscher, R.M., McConnell, E.E. and New, A.E.: Enzootic Brucella canis - an occult disease in a research canine colony. Lab. Lab. Anim. Sci. 24:769-799, 1974.

27. Stuart, D.D., Buck, G.E. and McConnell, E.E.: Necrotic dermatitis of mice caused by Lancefield Group G. Streptococci. Lab. Anim. Sci. 25:296-302, 1975.

28. McNutt, N.S., Amster, R.L., McConnell, E.E. and Morris, F.: Hepatic pathology in mice after continious inhalation exposure to 1,1,1-trichloroethylene. Lab. Invest. 32:642-654, AMRL-TR-74-60, 1975.

29. Thigpen, J.E., Faith, R.E., McConnell, E.E. and Moore, J.A.: Increased susceptibility to bacterial infection as a sequela of exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Infect. Immun. 12:1319-1324, 1975.

30. McConnell, E.E. and Talley, F.A.: Intracytoplasmic hyaline globules in the adrenal medulla of laboratory animals. Vet. Path. 14:435-440, 1977.

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32. McConnell, E.E., Moore, J.A. and Dalgard, D.W.: Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in rhesus monkeys (Macaca mulatta) following a single oral dose. Toxicol. Appl. Pharmacol. 43:175-187, 1978.

33. Hass, J.R., McConnell, E.E. and Harvan, D.J.: Chemical and toxicologic evaluation of Firemaster BP-6: a preliminary report. J. Agr. Food Chem. 26:94-99, 1978.

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16. Solleveld, H.A. and McConnell, E.E.: Time-age associations in experimental oncogenesis. Third International Symposium of the Society of Toxicologic Pathologists, Arlington, VA, 1984.

17. McConnell, E.E.: Quality and the National Toxicology Program. NTP - Industry Joint Conference on Managing Conduct and Data Quality of Toxicology Studies, Raleigh NC, 1985.

18. McConnell, E.E.: Guidelines for Combining Neoplasms for Evaluation of Rodent Carcinogenesis Studies. International Life Sciences Institute Histopathology Seminar, Hanover, Germany, 1985.

19. Adkins Jr., B., McConnell, E.E.: Inhalation Carcinogenesis Study of Wollastonite in Rats. Second U.S.-Dutch International Symposium: Aerosols, Williamsburg, Virginia, 1985.

20. McConnell, E.E.: Options for Aggregation of Incidence Data. Interdisciplinary Discussion Group on Carcinogenicity Studies, Chapel Hill, North Carolina, 1986.

21. McConnell, E.E.: Fiber Toxicity: Beyond the Stanton Hypothesis. American Society of Mining Engineers, Phoenix, Arizona, 1988.

22. McConnell, E.E., Hejtmancik, M., Peters, A.C., Persing, R. Chronic Toxicity of Pentachlorophenol. Ann. Meet., Soc. Toxicol., Atlanta, GA., 1989.

23. Adkins, B., McConnell, E.E., Hall, L. Carcinogenicity Studies of Wollastonite in Rats. Ann. Meet., Soc. Toxicol., Atlanta, GA., 1989.

24. McConnell, E.E., Hasemena, J.A. and Boorman, G.A.: Proliferative Lesions of the Thyroid Gland: A Review of the National Toxicology Program Data Base. Ann. Meet., Soc. Toxicol., Maimi, FL., 1990.

25. McConnell, E.E. Comparative Responses in Carcinogenic Bioassays as a Function of Age at First Exposure. in Similarities and Differences Between Children and Adults: Implications for Risk Assessment, ILSI/RSI, Hunt Valley, MD, November, 1990.

26. Hesterberg, T.W., Mast, R., McConnell, E.E., Vogel,O., Chevalier, J., Bernstein, D.M. and Anderson, R. Chronic Inhalation Toxicity and Oncogenicity Study sof Refractory Ceramic Fibers (RCF) in Fischer 344 Rats. Ann. Meet., Soc. Toxicol., Dallas, TX, 1991 also The Toxicologist 11:85 (254), 1990.

27. McConnell, E.E., Hesterberg, T.W., Hadley, J.G., Bernstein, D.M. and Mast, R.W. A Comparison of the Effects of Chrysotile and Crocidolite Asbestos in Rats After Inhalation for 10 Months. Ann. Meet., Soc. Toxicol., Seattle, WA, 1992, also The Toxicologist 12:90 (274), 1992.

28. Glass, L.R., Mast, R.W., Hesterberg, T.W., Anderson, R. and McConnell, E.E. Inhalation Oncogenicity Study of Refractory Ceramic Fiber (RCF) in Rats -- Final Results. Ann. Meet., Soc. Toxicol., Seattle, WA, 1992, also The Toxicologist 12:377 (1477), 1992.

29. Mast, R.W., McConnell, E.E., Glass, L.R., Hesterberg, T.H., Anderson, R. and Bernstein, D.M. Inhalation Oncogenicity Study of Kaolin Refractory Ceramic Fiber (RCF) -- Final Results. Ann. Meet., Soc. Toxicol., Seattle, WA, 1992, also The Toxicologist 12:377 (1478), 1992.

30. McConnell, E.E., Chevalier, J., Hesterberg, T.W., Hadley, J.G., and Mast, R.W. A Comparison of the Effects of Chrysotile and Crocidolite Asbestos in Rats after Inhalation. in Toxicologic and Carcinogenic Effects of Solid Particles in the Respiratory Tract. 4th International Inhalation Symposium, Hannover, Germany, 3 March 1993.

31. Hesterberg, T.W., Miiller, W.C., McConnell, E.E., Hadley, J.G., Bernstein, D.M., Thevenaz, P. and Anderson, R. Chronic Inhalation Toxicity of Fibrous Glass in Rats. in Toxicologic and Carcinogenic Effects of Solid Particles in the Respiratory Tract. 4th International Inhalation Symposium, Hannover, Germany, 3 March 1993.

32. Mast, R.W., Glass, L.R., McConnell, E.E., Hesterberg, T.W., and Anderson, R. Chronic Inhalation, Intratracheal and Biopersistence Studies of Refractory Ceramic Fibers. in Toxicologic and Carcinogenic Effects of Solid Particles in the Respiratory Tract. 4th International Inhalation Symposium, Hannover, Germany, 3 March 1993.

33. Mast, R.W., McConnell, E.E., Glass, L.R. and Hesterberg, T.W. A Multiple Dose Chronic Inhalation toxicity Study of Kaolin Refractory Ceramic Fiber (RCF) in Male Fischer 344 Rats. The Toxicologist 13:43 (63), 1993.

34. McConnell, E.E., Hesterberg, T.W., Hadley, J.G., and Mast, R.W. A Comparison of the Effects of Chrysotile and Crocidolite Asbestos in Rats after Inhalation - 24 Month Results. The Toxicologist 13:43 (67), 1993.

Oral Presentationsv/Invited Lectures:

1. "Lymphosarcoma in Domestic Animals," Armed Forces Institute of Pathology, Washington, DC, March 1966.

2. "The Clinician and Pathologist," South Africa VMA (WITS) Congress, May 1970.

3. "Experiences with Animals at the Kruger National Park," Veterinary Faculty, Onderstepoort, September 1970.

4. "The Role of a Veterinarian in the U.S. Air Force," Eastern Transvaal Veterinary Medical Association, Pietersburg, October 1970.

5. "Anthrax in an African Buffalo from the Kruger National Park," Congress of the South African VMA, September 1971.

6. "Respiratory Acariasis in Chacma Baboons," Science Week-1972, WITS University, Johannesburg, June 1972.

7. "Pathological Observations in 100 Baboons from the Kruger National Park," Veterinary Faculty and Staff of the Veterinary Research Institute, Onderstepoort, July 1972.

8. "Lesions in Free-Ranging Baboons," Pathology of the Diseases of Laboratory Animals, Armed Forces Institute of Pathology, September 1972.

9. "Lesions Found in Animals Exposed to Coal Tar Aerosols," 4th Annual Conference on Environmental Toxicology, Wright-Patterson AFB, September 1973.

10. "Anthrax in an African Buffalo," American College of Veterinary Pathologists Annual Meeting, San Antonio, TX, December 1973.

11. "The Comparative Toxicity of Chlorinated Dibenzo-p-dioxin Isomers in Mice and Guinea Pigs," Society of Toxicology Annual Meeting, Atlanta, GA, March 1976.

12. "The Toxicopathology of TCDD," Workshop on TCDD, Milan, Italy, October 1976.

13. "Toxicological Research Programs at the National Institute of Environmental Health Sciences," University of California, Davis, October 1977.

14. "Training of Comparative Pathologists for a Career in Toxicology," University of California, Davis, October 1977.

15. "Exquisite Toxicity in the Guinea Pig to Structurally Similar Halogenated Dioxins, Furans, Biphenyls and Naphthalenes," 17th Annual Meeting, Society of Toxicology, San Francisco, CA, March 1978.

16. "Toxicopathology Characteristics of Halogenated Aromatics," Science Week, New York Academy of Sciences, New York, NY, June 1978.

17. "Pathology and Toxicology of Chlorodibenzodioxins in Laboratory Animals," Ohio State University, Columbus, OH, May 1979.

18. "Chronic Toxicity of Technical and Analytical Grade Pentachlorophenol in Cattle," Ohio State University, Columbus, OH, May 1979.

19. "Comparative Toxicity of Related Halogenated Hydrocarbons," Armed Forces Institute of Pathology, Washington, DC, May 1979.

20. "The Toxicology of Dibenzofurans and Dibenzodioxins," 45th Meeting of the Interagency Collaborative Group on Environmental Carcinogenesis, National Cancer Institute, Bethesda, MD, May 1979.

21. "Comparative Toxicity of Technical and Analytical Pentachlorophenol in Cattle," NIEHS Science Fair, North Carolina State University, Raleigh, NC, June 1979.

22. "The Lesions Induced by Related Halogenated Aromatics in Various Species of Animals," 1979 Wildlife Disease Association Meeting, University of Oklahoma, Norman, OK, August 1979.

23. "Essentials of Routine Pathotoxicology Evaluation," Consensus Development of Immunotoxicology Meeting, NIEHS, Research Triangle Park, NC, November 1979.

24. "Toxicopathological Syndrome Induced by Related Halogenated Polycyclic Hydrocarbons," Ohio Agricultural Research and Development Center, Wooster, OH, August 1980.

25. "The National Toxicology Program," Conservative Trends in Laboratory Animal Science, Eighth Annual District IV AALAS Seminar, Raleigh, NC, March 1981.

26. "NTP Testing Results with Emphasis on Bioassays of DEHP, DEHA and Butyl Benzyl Phthalate," Phthalate Ester Conference, Washington, DC, June 1981.

27. "Effects of Subchronic Chlordecone Exposure on the Fertility of Female Rats," North Carolina Chapter of the Society of Toxicology, Research Triangle Park, NC, January 1982.

28. "Evaluation of Pathology Requirements," Third Annual Meeting of the American College of Toxicology, Washington, DC, December 1982.

29. "NIEHS Asbestos Feeding Study - Hamsters and Rats," Summary Workshop on Ingested Asbestos, USEPA, Cincinnati, OH, November 1982.

30. "Histopathology Workload in Carcinogenesis Bioassays - How much is necessary?" The Toxicology Forum Annual Winter Meeting, Arlington, VA, February 1983.

31. "Proliferative Lesions of the Exocrine Pancreas in Male F344 Rats - The Effect of Corn Oil," The Toxicology Forum 1983 Annual Winter Meeting, Arlington, VA, February 1983.

32. "Toxic Oil Syndrome," WHO Meeting, Madrid, Spain, March 1983.

33. "An Improved Protocol for Bioassay Studies," 2nd International Symposium of the Society of Toxicologic Pathologists, Crystal City, VA, May 1983.

34. "Chronic Toxicity of PCBs and Related Compounds in Various Animal Species," CCERP Conference on Potential Health Effects of Polychlorinated Biphenyls and Related Persistent Halogenated Hydrocarbons, NIEHS, Research Triangle Park, NC, September 1983.

35. "Toxicity of PCBs, Polychlorinated Dibenzofurans and Dibenzodioxins," International Workshop on Occupational Hazards Caused by Polychlorinated Biphenyls (PCBs) and Chlorobenzenes in Capacitors and Transformers, Espoo, Finland, September 1983.

36. "Dioxins in the Environment," Human Health and Toxicity Workshop, Michigan State University, East Lansing, MI, December 1983.

37. "Toxic and Carcinogenic Responses in Experimental Animals Administered Dibenzo-p-dioxins and Dibenzofurans," Federation of American Societies for Experimental Biology, St. Louis, MO, April 1984.
38. "Lesions in Animals Exposed to EDB," North Carolina Chapter of the Society of Toxicology Spring Meeting, Durham, NC, April 1984.

39. "Studies on the Bioavailability in Guinea Pigs of Dioxin in Soil," Society of Toxicology Meeting, Atlanta, GA, March 1984.

40. "NTP Program Update," European Toxicology Forum, Geneva Switzerland, September 1984.

41. "The Response of NTP to the Recommendations of the Ad Hoc Panel," 15th Conference on Environmental Toxicology, Dayton, Ohio, October 1984.

42. "National Toxicology Program Status and New Initiatives," The Toxicology Forum 1985 Annual Winter Meeting, Washington, D.C., February 1985.

43. "Relevant Non-Statistical Bioassay Issues," Symposium on Long-Term Animal Carcinogenicity Studies: A Statistical Perspective, American Statistical Association, Washington, D.C., March 1985.

44. "The Short and Long Term Health and Environmental Impacts," Conference on the Implications of the Bhopal Tragedy, The Workers Policy Project, Newark, New Jersey, March 1985.

45. "Ad Hoc Report on Chemical Carcinogenesis Testing and Evaluation," Environmental Health Seminar, University of Cincinnati, Ohio, May 1985.
46. "Challenges and Opportunities for Pathologists in the National Toxicology Program," ILSI Histopathology Seminar on the Reproductive System of Laboratory Animals, Hanover, Germany, September 1985.

47. "The Justification for Combining Benign and Malignant Tumors (or Not Combining Them) in Statistical Analysis Lesions in the Rat," ILSI Histopathology Seminar on the Reproductive System of Laboratory Animals, Hanover, Germany, September 1985.

48. "Methyl Isocyanate - Preliminary Study Results," ILSI Histopathology Seminar on the Reproductive System of Laboratory Animals, Hanover, Germany, September 1985.

49. "Overview of the National Toxicology Program in the United States and Findings in Selected Studies," C.L. Davis Sixth Annual Symposium, Cheshire, England, September 1985.

50. "Carcinogenesis Studies Results from the U.S. National Toxicology Program and the U.S. National Cancer Institute: 1976-1985," Collegium Ramazzini, Living in a Chemical World, Bologna, Italy, October 1985.

51. "Methylene Chloride, Methylchloroform and Trichloroethylene," Collegium Ramazzini, Living in a Chemical World, Bologna, Italy, October 1985.

52. "Liver Foci Formation During Aflatoxin Carcinogenesis in Rat: A Quantitative Study," Collegium Ramazzini, Living in a Chemical World, Bologna, Italy, October 1985.

53. "The Toxicity of Methyl Isocyanate in Rats and Mice," New Delhi and Madras, India, February 1986.

54. "Response to the Integration of Recommendations of the Ad Hoc Panel on Carcinogenesis Testing and Evaluation," Society of Toxicology Annual Meeting, New Orleans, La., 1986.

55. "NTP Strategy for Combining Neoplasms for Evaluation of Carcinogenesis Studies," Office of Pesticides & Toxic Substances Seminar Program, EPA, Washington, D.C., April 1986.

56. "Environmental Toxicology in the Mid-Eighties: Interfacing with the Toxicologist," FASEB 70th Annual Meeting, St. Louis, Missouri, April 1986.

57. "NTP's Response to the Ad Hoc Panel Recommendations," FEMA Annual Meeting, Palm Beach, Florida, April 1986.

58. "Studies on the Toxicity of Methyl Isocyanate, the Chemical Responsible for the Bhopal Disaster," North Carolina State University Microbiology Seminar Series, Raleigh, North Carolina, April 1986.

59. "Options for Aggregation of Incidence Data," Interdisciplinary Discussion Group on Carcinogenicity Studies (ILSI NF), Chapel Hill, North Carolina, June 1986.

60. "NTP Evaluation of Experimental Studies," The Toxicology Forum 1986 Annual Summer Meeting, Aspen, Colorado, July 1986.

61. "NTP Response to the Report of the Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation," The Toxicology Forum 1986 Annual Summer Meeting, Aspen, Colorado, July 1986.

62. "Inhalation Study of Wollastonite in Rats," SAE's 4th Annual Colloquium on Brakes, Atlantic City, NJ, October, 1986.

63. "Considerations in Determining the Estimated Maximum Tolerated Dose," Pharmaceutical Manufacturers' Association Drug Safety Subsection meeting, Nashville, TN, November, 1986.

64. "Current Status of the Issue of Maximum Tolerated Dose (MTD) within the U.S. National Toxicology Program," 26th Annual Meeting of the Society of Toxicology, Washington, D.C., February, 1987.

65. "Federal Perceptions of Board Certification," Spring Meeting and Reception for Members of Association of Government Toxicologists, Bethesda, MD, May, 1987.

66. "Gavage Studies in Mice and Rats," Paradichlorobenzene Symposium (Sponsored by CIIT and Chlorobenzene Producers Association), Washington, D.C., July 1987.

67. "NTP Database," Meeting of the Ad Hoc Working Group on Carcinogenicity Testing, Washington, D.C., July 1987.

68. Rapporateur at Mouse Liver and Rat Kidney Tumors Workshop, EPA Science Advisory Board, Environmental Health Committee and Halogenated Organics Subcommittee, Washington, D.C., August 1987.

69. "Toxicology Learned the Hard Way," Principles of Toxicology, Boston Univ., August, 1988.

70. "Mouse Liver Tumors: The Problem," Mouse Liver Carcinogenesis Conference, Austin, TX, November, 1988.

71. "Biology Issues in the Statistical Evaluation of Rodent Carcinogenicity Studies," Course on Biostatistics, International Agency for Research on Cancer, Lyon, France, December, 1988.

72. "Pitfalls in Carcinogensis Testing," North Carolina State University, Graduate Course VMS 643 "Rodent Toxicologic Pathology", December, 1988.

73. "Maximum Tolerated Dose: The Debate," Brookings Institute, Washington, D.C., May, 1989 and Research Triangle Chapter, Society for Risk Analysis, Research Triangle Park, NC, May, 1989.

74. "The Search for Adequate Bioassay Data: Crude Biology Versus Statistics," Trace Substances in Environmental Health, Annual Meeting of the Society for Environmental Geochemistry and Health, Cincinnati, OH, May, 1989.

75. "Animal Bioassays: Using Protocols and Interpreting Results," Regional Risk Assessment Workshops, Workshop 1, Chicago,IL, June, 1989; Atlanta, GA, December 1989.

76. "Target Organ Toxicity in Carcinogenesis," Annual Summer Toxicology Forum, Aspen, CO, July, 1989.

77. "Toxicity Testing and Evaluation - Pratical Considerations," International Training Workshop on Risk Assessment and Management, Chulabhorn Research Institute, Bangkok, Thailand, December 1989.

78. "Update on the Search for Adequate Bioassay Data: Crude Biology Versus Statistics," Annual Meeting of the Society of Toxicology, Miami, FL, February, 1990.

79. "Biological Effects of Dietary Restriction: An International Conference", Washington, D.C., March 1990.

80. "Principles of Route-to-Route Extrapolation," (Rapporteur), Hilton Head, SC, March 1990.

81. "Molecular Mechanisms of Fiber Cytotoxicity and Carcinogenesis," Banbury Center, Cold Spring Harbor Laboratory, NY, March 1990.

82. "NTP Carcinogens - Interpretational Problems," International Workshop: Early Indicators of Non-genotoxic Carcinogenesis, World Health Organization, Brussels, Belgium, June 1990.

83. "Principles of Carcinogenesis," School of Pharmacy, Cambell University, Buies Creek, NC, October, 1990.

84. "Comparative Responses in Carcinogenesis Bioassays as a Function of Age at First Exposure," Similarities and Differences Between Children and Adults: Implications for Risk Assessment, ILSI/RSI, Hunt Valley, MD, November, 1990.

85. "Ethylene Thiourea: A Case Study," Similarities and Differences Between Children and Adults: Implications for Risk Assessment, ILSI/RSI, Hunt Valley, MD, November 1990.

86. "Problems and Considerations in the Design and Interpretation of Rodent Carcinogenesis Studies", Lectures as part of "Toxicologic Pathology" course, VMS 643, College of Veterinary Medicine, NCSU, December, 1990.

87. "Toxicologic Studies", Man-made Mineral Fibers: Status of Health Risk Assessment", Johns Hopkins University, March, 1991.

88. "Fiber Toxicity - Background and Historical Perspective", Society of Toxicologic Pathologists, Research Triangle Park, May 1991.

89. "Animal Bioassay Issues/Use of QRA", International Society of Regulatory Toxicology and Pharmacology workshop "A Review of Risk Assessment and OMB's Report on its Application in Regulatory Agencies", Crystal City, VA, June 1991.

90. "The Design, Conduct and Interpretation of Fiber Toxicity Studies", A. L. Bortree Lecture Series, Veterinary Science Dept., Pennsylvania State University, PA, September 1991.

91. "Fiber Toxicology in Experimental Animals: Results of Studies with Natural and Man-Made Mineral Fibers", Intramural Fiber Research Workshop, National Institute for Occupational Safety and Health, Morgantown, WVA, September 1991.

92. "Conduct and Interpretation of Inhalation Studies of the Toxicity and Carcinogenicity of Man-Made Fibers", Workshop: Approaches to Evaluating the Toxicity and Carcinogenicity of Man-Made Fibers. Durham, NC, November 1991.

93. "Man-Made Fibers: Review of Toxicology Data", '92 Annual Toxicology Forum, Washington, D.C., February 1992.

94. Invited testimony before the German MAK Commission on MMVF's. Munich, Germany, May 1992.

95. "Man-Made Fibres: Validity of Methods for Assessment of Carcinogenicity of Fibres", WHO Regional Office for Europe, Copenhagen, 19-20 May, 1992.

96. "Evaluation of Reduced Protocols for Carcinogenicity Testing of Chemicals", EPA, Washington, DC, 22-23 Sept 1992.

97. "Comparative Pathology of Chrysotile and Crocidolite Asbestos", TIMA/NAIMA Fiber Science Workshop, St. Petersberg, FL, 20 Jan 1993.

98. "Relationship Between Pulmonary Fibrosis and Cancer", TIMA/NAIMA Fiber Science Workshop, St. Petersburg, FL, 20 Jan 1993.

99. "The Toxicologic Pathologist in 2000 A.D.: Needs for Industry, Government and Academia", Role of Toxicologic Pathology in Safety Assessment. National Academy of Science, Washington, DC, 10 Feb 1993.

100. "A Comparison of the Effects of Chrysotile and Crocidolite Asbestos in Rats after Inhalation", Toxicologic and Carcinogenic Effects of Solid Particles in the Respiratory Tract. 4th International Inhalation Symposium, Hannover, Germany, 3 March 1993.

101. "Styrene/styrene oxide - Results of animal carcinogenicity studies", International Symposium on Health Hazards of Butadiene and Styrene, Helsinki, Finland, 21 April 1993.

102. "The Impact of Toxicity Studies in the Regulatory Process", Dept. of Toxicology Seminar Series, Michigan State University, 3 June 1993.

103. "The Toxicopathology of Inhaled Fibers", Department of Pathology, Michigan State University, 3 June 1993.

104. "Peer Review in Carcinogenicity Bioassays - Uses/Abuses", Society of Toxicologic Pathologists 12th International Symposium, Alexandria, VA, 28 June 1993.

105. McConnell, E.E., Kamstrup, O., Musselman, R., Hesterberg, T.W., Chevalier, J. and Thevenaz, P. Chronic Inhalation Study of Size-separated Man-made Vitreiys Fibers in Fischer 344/N Rats. 24th International Congress on Occupational Health, Nice, France, 30 October 1993.

106. McConnell, E.E. Invited expert testiimony before the German Ministry of the Environment on MMVF's. Berlin, Germany, 9-10 December 1993.

107. McConnell, E.E. 'Fiber-induced pathology in experimental animals. Physiology and Cell Biology Conference, University of Rochester Pulmonary and Critical Care Unit, 20 December 1993.

CURRICULUM VITAE

Name: Jerrold Michael Ward

Date of Birth: October 29, 1942

Citizenship: United States

Marital Status: Married, 2 Children

Education:

1966	D.V.M.	Cornell University, Ithaca, New York
1970	Ph.D.	Comparative Pathology, University of California, Davis

Chronology of Employment:

1966 - 1970	Research Pathologist and NIH Trainee, Department of Veterinary Pathology, School of Veterinary Medicine University of California, Davis
1970 - 1971	Supervisory Veterinary Medical Officer, Bureau of Radiological Health, DHEW, PHS, Rockville, MD
1971 - 1972	Supervisory Veterinary Medical Officer (Veterinary Pathologist), Division of Research and Monitoring, Radiation Programs, Environmental Protection Agency, Rockville, MD
1972 - 1974	Supervisory Veterinary Medical Officer (Veterinary Pathologist), Carcinogen Metabolism and Toxicology Branch, Carcinogenesis, Division of Cancer Cause and Prevention, (DCCP), National Cancer Institute (NCI), National Institutes of Health (NIH), Bethesda, MD
1974 - 1977	Supervisory Veterinary Medical Officer (Veterinary Pathologist), Laboratory of Toxicology, Division of Cancer Treatment, NCI, NIH, Bethesda, MD
1977 - 1978	Veterinary Medical Officer (Veterinary Pathologist), Tumor Pathology Branch, Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, NCI, NIH, Bethesda, MD

1979 - 1981	Chief, Tumor Pathology, National Toxicology Program, NCI, NIH, Bethesda, MD
1981-1992	Chief, Tumor Pathology and Pathogenesis Section, Laboratory of Comparative Carcinogenesis, Division of Cancer Etiology, NCI, Frederick, MD
1992-	Chief, Veterinary and Tumor Pathology Section, Office of Laboratory Animal Science, Office of The Director, National Cancer Institute, Frederick, MD

Teaching Experience:

1968 - 1970	Graduate Assistant, Department of Veterinary Pathology, School of Veterinary Medicine, University of California- Davis
1975 - 1980	Faculty, Foundation for Advanced Education in the Sciences, Comparative Pathology Course, Bethesda, Maryland
1978 - 1980	The Center for Professional Advancement, Carcinogenesis/ Mutagenesis Course, East Brunswick, New Jersey
1979	Lecturer, Department of Pathology, Uniformed Services University of the Health Sciences, Bethesda, Maryland
1981 - 1985, 1990-	Lecturer, Neoplasms of Rats, Armed Forces Institute of Pathology course on Pathology of Laboratory Animals, Washington, D.C.
1981 - 1982	Adjunct Associate Professor of Pathology, The George Washington University School of Medicine and Health Sciences, Washington, D.C.
1981	Faculty, Endocrine Histopathology of Laboratory Animals Seminar, International Life Sciences Institute (ILSI) and Institute of Experimental Pathology, Hannover Medical School, Hannover, West Germany
1982	Faculty, Neoplastic and Nonneoplastic Lesions in Mice, Intox Laboratories, Arlington, Virginia, June, 1982
1983	Faculty, ILSI and Nara Medical University, Endocrine Histopathology Seminar, Nara, Japan
1983	Faculty, ILSI and Harvard Medical School, Endocrine Histopathology Seminar, Boston, Massachusetts
1988	Faculty, ILSI and Hannover Medical School, Hemopoietic Histopathology Seminar, Hannover, West Germany
1990	Faculty, ILSI and Nara Medical University, Hemopoietic Histopathology Seminar, Nara, Japan

Professional Organizations:

Diplomate, American College of Veterinary Pathologists
American Veterinary Medical Association
International Academy of Pathology
American Association for Cancer Research
Society of Toxicologic Pathologists

Awards/Honors:

1966	Cornell University Clinical Conference Award
1974	National Academy of Sciences Travel Grant to the International Cancer Congress, Florence, Italy
1979	Special Achievement Group Award, NCI Carcinogenesis Testing Program
1984	Commissioner's Special Citation, Food and Drug Administration
1986	Research Fellowship, Foundation for Promotion of Cancer Research, Tokyo, Japan
1994	Patent Application: *Helicobacter hepaticus* and related methods. Serial No. 08/266,414
1995	NIH Director's Award

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Home Address: 10513 Wayridge Drive, Montgomery Village, MD 20879

Employment Address: NCI-FCRDC, Fairview 201, Frederick, MD 21702-1201
Telephone: 301-846-1239 FAX 301-846-6389
Email: Ward@ncifcrf.gov

Service on Boards or Committees:

1975 - 1981	Editorial Board, *Veterinary Pathology*
1976 - 1978	Chairman and Organizer, Viral Specialty Group, American College of Veterinary Pathologists
1978	Member, Education Committee - Carcinogenesis Program, American College of Veterinary Pathologists
1979 - 1985	Co-Chairman, Infectious Disease Specialty Group, American College of Veterinary Pathologists
1981 -	Editorial Board, *Pathology of Laboratory Animals* (International Life Sciences Institute - ILSI)
1987 - 1989	Co-editor, *Pathology of Laboratory Animals - Hemopoietic System* (ILSI)
1988 -	Editorial Board, *Age-Associated Changes in Laboratory Animals* (ILSI)
1988 - 1991	Editorial Board, *Experimental Pathology*
1990 - 1995	Editorial Board, *Toxicologic Pathology*
1991 -	Editorial Board, *Experimental and Toxicologic Pathology*
1992-	Editorial Board, *Veterinary Pathology*
1994-95	Society of Toxicologic Pathologists Program Committee
1995-	Section Editor, Safety Assessment, *Toxicologic Pathology*

Professional Advisory and Consultant Activities:

Member, Discussion Group-Criteria for Tumor Diagnosis and Classification of Malignancy. Conference on Carcinogenesis Testing in the Development of New Drugs, May 23-25, 1973, Washington, D.C., National Academy of Sciences.

Member, FDA, FD&C Red No. 40 Second Interim Working Group, December, 1977-1981.

Consultant and Expert Witness, FDA Hearing on Denial of Petition for Listing of FD&C Red No. 4 for Use in Marishino Cherries and Ingested Drugs, April 12, 1978, Rockville, Maryland.

Member, FDA Interagency Committee on Nitrite Research, 1978-1980.

Member, Project Group on Standardization of Measurements and Tests, Task Force on Cancer and Heart and Lung Disease, Environmental Protection Agency, 1979.

Consultant, Scientific Advisory Board, National Center for Toxicological Research, Jefferson, Arkansas, 1979.

Member, Mouse Lymphoma Study Group, 1979. Sponsored by the Nutrition Foundation.

Consultant, Division of Pathology, Bureau of Foods, Food and Drug Administration, 1978-1982.

Member, Working Group on Evaluation of Carcinogenic Risk of Chemicals to Man, International Agency for Research in Cancer, Lyon, France, February 10-17, 1981.

Consultant and Expert Witness, FDA Hearing on Proposal to Withdraw Approval of Certain New Animal Drug Applications: Furazolidone (NF-180), Nitrofurazone (NF-7), & Furaltadone (NF-260), 1978-1985.

Alternate Member, TSCA Interagency Testing Committee, 1981-1983.

Consultant, Carcinogen Identification and Risk Assessment Branch, Occupational, Safety and Health Administration, Dept. of Labor, Washington, D.C., 1979-1981.

Expert Witness, State of California, Department of Health, OSHA, Sacramento, California, November 12, 1981, Hearing on Standards for Occupational Exposure Levels to 1,2-Dibromoethane.

Consultant, Chemical Pathology Branch, National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, 1982-1983.

Expert Witness, Occupational Safety and Health Administration, U.S. Department of Labor, Informal Public Hearing on Occupational Exposure to Ethylene Oxide, Washington, D.C., July 26, 1983.

Member, Consensus Workshop on Formaldehyde - Carcinogenicity, Histopathology, Genotoxicity Panel, Food and Drug Administration, National Center for Toxicological Research, Little Rock, Arkansas, October 3-6, 1983.

Expert Witness, Melvin D. Reuber v. United States of America, Washington, D.C., May 3, 1984.

Ad Hoc Consultant, National Toxicology Program, Peer Review Bioassay Panel, July 26, 1984.

Member, Committee on the Carcinogenicity of Cyclamates, 1984-1985, National Research Council, National Academy of Sciences.

Member, Color Additive Scientific Review Panel, FDA, 1985.

Co-Organizer, US-Japan Seminar on "Development of New-Medium-Term Bioassays for Carcinogens," US-Japan Cooperative Cancer Research Program, Honolulu, Hawaii, December 15-17, 1987.

Organizing Committee, Conference on "Mouse Liver Carcinogenesis," Austin, Texas, November 30-December 3, 1988.

Member, Working Group on Whole-Animals Tests, Workshop on "Research to Improve Predictions of Long-Term Chemical Toxicity," National Research Council, Board on Environmental Studies and Toxicology, National Academy of Sciences, 1989.

Review Panel, Lymphoreticular System, Tumor Pathology Information System for Toxicologists, IARC, 1991-

Advisory Panel, Nomenclature for Spontaneous and Chemically-Induced Lesions of Animals, National Institute of Hygienic Science, Tokyo, Japan, 1991-

Consultant, Division of Drug Products, Center for Drug Evaluation and Research, Food and Drug Administration, 1992-

Member, National Toxicology Program Board of Scientific Counselors, Technical Reports Review Subcommittee, 1992-

Member, Panel, Hematopoietic System, International Classification of Rodent Tumours, Part 1, The Rat, International Agency for Research in Cancer, World Health Organization, 1992.

Member, Consultant, Cardiovascular & Renal Drugs Advisory Committee, Nonprescription Durgs Advisory Committee, Office of Over-The-Counter Drug Evaluation, Food and Drug Administration, Rockville, MD, July 27, 1994

Member, Panel, Digestive System, International Classification of Rodent Tumours, Part 1, The Rat, International Agency for Research in Cancer, World Health Organization, 1994.

Member, Ad Hoc Working Group, Criteria for Selecting Substances Nominated for Listing in the DHHS PHS Biennial Report on Carcinogens, NTP Board of Scientific Counselors, 1995-

U. S. Public Health Service Contract Experience: Project Officer or Co-Project Officer:

Bioassay of Environmental Chemicals, Bio-Research, Cambridge, MA, 68-1311, 1972 (Co-P.O.)

Bioassay of Environmental Chemicals, Dow Chemical Co., Indianapolis, IN, 72-3254, 1972-73 (Co-P.O.)

Bioassay of Environmental Chemicals, Hazleton Labs., Inc., Vienna, VA, 70-2209, 72-3278, 1972-74 (Co-P.O.)

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CORNING Hazleton

STATISTICAL ANALYSES OF $B_6C_3F_1$ MOUSE LIVER TUMORS FOR THE TOXAPHENE STUDY

(PWG CONSENSUS HISTOPATHOLOGY)

CHV STUDY NO. 116-194

Purpose:

The purpose of this report is to present the statistical analyses of the liver tumor histopathology evaluation by the Pathology Working Group (PWG) consensus reading from the "Bioassay of Toxaphene for Possible Carcinogenicity" in male and female $B_6C_3F_1$ mice (1). The PWG consisted of Drs. Jerry F. Hardisty, Russell C. Cattley, Michael R. Elwell, Joel R. Leininger, Ernest F. McConnell, and Jerrold M. Ward. The above mentioned study was conducted by the National Cancer Institute (Cas No. 8001-35-2, NCI-CG-TR-37, 1979) with the following design:

	Male			Female		
Dose (ppm)#	0	99	198	0	99	198
Initial No. of Animals	10	50	50	10	50	50

The dose levels varied during the 90-week administration of Toxaphene. The levels presented here are in terms of time weighted averages.

Method:

Several sets of statistical analyses consistent with the original ones were performed on the re-evaluation of the slides. They consisted of unadjusted analysis using Cochran-Armitage test for trend and Fisher-Irwin exact test for group comparisons (2) with the number of tumor bearing animals in the numerator and the number of animals at risk in the denominator for each group. The number at risk here includes all the animals whose tissues were histopathologically evaluated. The following list shows the animals with missing tissues that were not included in the analyses for both sexes:

	Male	Female
Matched Control	238,258	
99 ppm		250
198 ppm	353,366,393,394	311,319,326

A second set consisted of gross adjusted analysis using the same methods as above. For this purpose, all animals dying prior to the occurrence of the first liver adenoma and/or carcinoma (Week 59) in any group were excluded from being at risk as shown below:

	Male	Female
Concurrent Control		021
Matched Control	236,256,280	086
99 ppm	279	
198 ppm	376	307

Additionally, survival adjusted analyses were performed with all animals at risk using both logistic regression of tumor prevalences (3) and interval based IARC method (4). For the IARC method, exact analyses (4) were performed whenever the total number of tumor bearing animals were <20. The intervals selected were based on the current NTP (National Toxicology Program) scheme: o-52 weeks, 53-78 weeks, 79-90 weeks, and terminal sacrifice interval. Since the number of animals (10) in the concurrent study control group in each sex was too small, all analyses also used control data from four other studies (Gardona, Malathion, Lindane, and Phosphamidon) conducted by the National Cancer Institute during approximately the same time frame. Including the concurrent control with these four matched controls provides a pooled control of approximately 50 mice/sex to achieve adequate power of statistical tests for these tumor data. Although these four additional studies may have lasted slightly longer than the Toxaphene study, it was assumed that such small longer durations would not bias the matched control. Also, extra-binomial variations because of such matching was ignored in the spirit of the original statistical analyses conducted by the National Cancer Institute.

In each case, adenoma and carcinoma incidences were analyzed first separately and then combined as suggested by McConnell et al (6).

For all statistical analyses, one-sided tail probabilities were used for evaluation of the data. Continuity corrected statistics were used for computing these tail probabilities along with exact probabilities whenever necessary. The results are presented in Tables 1 (male) and 2 (female). In each case, the p-value under each of the two controls is for monotonic trend and the ones under the treated groups are for respective control versus treated group comparisons.

The following notations are used in this report to designate statistical significance:

** = Significant at $p \leq 0.01$
* = Significant at $p \leq 0.05$
↑ = Effect in the positive direction
↓ = Effect in the negative direction

Table 1
Results of the Statistical Analyses of Liver Adenoma and Carcinoma : Male

Tumor Type	Concurrent Cntrl	Pooled Cntrl	99 ppm	198 ppm
Liver: Adenoma	2/10	5/48	30/50	42/46
Unadjusted Analysis				
One-sided p-value	0.0000 ↑**		0.0236 ↑*	0.0000 ↑**
One-sided p-value		0.0000 ↑**	0.0000 ↑**	0.0000 ↑**
Gross Adjusted				
One-sided p-value	0.0000 ↑**		0.0201 ↑**	0.0000 ↑**
One-sided p-value		0.0000 ↑**	0.0000 ↑**	0.0000 ↑**
Logistic Prevalence				
One-sided p-value	0.0000 ↑**		0.0092 ↑**	0.0000 ↑**
One-sided p-value		0.0000 ↑**	0.0000 ↑**	0.0000 ↑**
IARC Interval Based				
One-sided p-value	0.0000 ↑**		0.0051 ↑**	0.0000 ↑**
One-sided p-value		0.0000 ↑**	0.0000 ↑**	0.0000 ↑**
Liver: Carcinoma	0/10	3/48	8/50	5/46
Unadjusted Analysis				
One-sided p-value	0.4071 ↑		0.2098 ↑	0.3586 ↑
One-sided p-value		0.2342 ↑	0.1128 ↑	0.3333 ↑
Gross Adjusted				
One-sided p-value	0.4007 ↑		0.2034 ↑	0.3512 ↑
One-sided p-value		0.2557 ↑	0.1279 ↑	0.3568 ↑
Logistic Prevalence				
One-sided p-value	0.4445 ↑		0.2235 ↑	0.3504 ↑
One-sided p-value		0.2971 ↑	0.1123 ↑	0.3379 ↑
IARC Interval Based				
One-sided p-value	0.6628 ↑		0.2476 ↑	0.4271 ↑
One-sided p-value		0.4861 ↑	0.1659 ↑	0.4164 ↑
Liver:Adenoma/Carcinoma	2/10	7/48	36/50	45/46
Unadjusted Analysis				
One-sided p-value	0.0000 ↑**		0.0032 ↑**	0.0000 ↑**
One-sided p-value		0.0000 ↑**	0.0000 ↑**	0.0000 ↑**
Gross Adjusted				
One-sided p-value	0.0000 ↑**		0.0025 ↑**	0.0000 ↑**
One-sided p-value		0.0000 ↑**	0.0000 ↑**	0.0000 ↑**
Logistic Prevalence				
One-sided p-value	0.0000 ↑**		0.0016 ↑**	0.0000 ↑**
One-sided p-value		0.0000 ↑**	0.0000 ↑**	0.0000 ↑**
IARC Interval Based				
One-sided p-value	0.0000 ↑**		0.0007 ↑**	0.0000 ↑**
One-sided p-value		0.0000 ↑**	0.0000 ↑**	0.0000 ↑**

Table 2
Results of the Statistical Analyses of Liver Adenoma and Carcinoma : Female

Tumor Type	Concurrent Cntrl	Pooled Cntrl	99 ppm	198 ppm
Liver: Adenoma	0/10	1/50	11/49	37/47
Unadjusted Analysis				
One-sided p-value	0.0000 ↑**		0.1041 ↑	0.0000 ↑**
One-sided p-value		0.0000 ↑**	0.0017 ↑**	0.0000 ↑**
Gross Adjusted				
One-sided p-value	0.0000 ↑**		0.1280 ↑	0.0000 ↑**
One-sided p-value		0.0000 ↑**	0.0021 ↑**	0.0000 ↑**
Logistic Prevalence				
One-sided p-value	0.0000 ↑**		0.1120 ↑	0.0000 ↑**
One-sided p-value		0.0000 ↑**	0.0035 ↑**	0.0000 ↑**
IARC Interval Based				
One-sided p-value	0.0000 ↑**		0.0757 ↑	0.0000 ↑**
One-sided p-value		0.0000 ↑**	0.0007 ↑**	0.0000 ↑**
Liver: Carcinoma	0/10	0/50	0/49	3/47
Unadjusted Analysis				
One-sided p-value	NT		NT	0.5542 ↑
One-sided p-value		NT	NT	0.1100 ↑
Gross Adjusted				
One-sided p-value	NT		NT	0.5786 ↑
One-sided p-value		NT	NT	0.1133 ↑
Logistic Prevalence				
One-sided p-value	NT		NT	0.4653 ↑
One-sided p-value		NT	NT	0.1084 ↑
IARC Interval Based				
One-sided p-value	NT		NT	0.6581 ↑
One-sided p-value		NT	NT	0.2878 ↑
Liver:Adenoma/Carcinoma	0/10	1/50	11/49	39/47
Unadjusted Analysis				
One-sided p-value	0.0000 ↑**		0.1041 ↑	0.0000 ↑**
One-sided p-value		0.0000 ↑**	0.0017 ↑**	0.0000 ↑**
Gross Adjusted				
One-sided p-value	0.0000 ↑**		0.1280 ↑	0.0000 ↑**
One-sided p-value		0.0000 ↑**	0.0021 ↑**	0.0000 ↑**
Logistic Prevalence				
One-sided p-value	0.0000 ↑**		0.1120 ↑	0.0000 ↑**
One-sided p-value		0.0000 ↑**	0.0035 ↑**	0.0000 ↑**
IARC Interval Based				
One-sided p-value	0.0000 ↑**		0.0757 ↑	0.0000 ↑**
One-sided p-value		0.0000 ↑**	0.0012 ↑**	0.0000 ↑**

Note: NT = Either there is no dose-response or equal proportions responding

Results:

As Table 1 indicates, there was a significant trend in the liver adenoma incidences in the male treated groups with concomitant significant increases in the 99 ppm and 198 ppm groups over both the concurrent and pooled control groups by any of the statistical tests used. Same effects were found in the combined adenoma and carcinoma incidences in the males. The carcinoma incidences alone did not indicate any significant trend or increase due to treatment.

In the females, from Table 2, there was a significant positive trend in the liver adenoma incidences when compared to the concurrent or pooled control by any of the tests used for the analyses. In this case, there was no significant increase in the 99 ppm group over the concurrent control although the increase in that group was significant versus the pooled control. The lack of significance in the 99 ppm group versus the concurrent control is due to lack of power because of small number at risk, 10, in the control group. The high dose incidence was significantly elevated when compared against both controls. The carcinoma incidences did not show any significant increase in any group versus any of the two controls. Once again, the combined adenoma and carcinoma incidences showed the same pattern as in the case of adenoma alone.

Discussion:

There were significant treatment related increases in liver adenoma and combined adenoma and carcinoma incidences in both male and female mice in this study, particularly when compared to the pooled control. The increases were associated with positive dose-response. The liver carcinoma incidences did not exhibit any significant increase or dose-response in either sex. In summary, statistical evaluation of liver tumors from this toxaphene study in $B_6C_3F_1$ mice showed significant dose-response and increase in treated groups for benign tumors against both concurrent and pooled controls in both male and female. There was no increase in malignant liver tumors in either sex of the study.

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5/6/96
Date

QUALITY ASSURANCE STATEMENT

Report Title: Statistical Analyses of $B_6C_3F_1$ Mouse Liver Tumors for the Toxaphene Study

Quality Assurance review of the statistical analyses report to the values provided was conducted according to the standard operating procedures of the Quality Assurance Unit and according to general Good Laboratory Practice regulations. This review was performed and findings were reported to the Principal Scientist and management as follows:

Dates of Inspection/Review	Dates Findings Reported	Inspector/Reviewer
Report Review: 04/13-14/96	04/15/96	D. Kuhn

Susan Weymouth
Susan Weymouth

5-2-96
Date Released

APPENDIX 5

SPONTANEOUS NEOPLASTIC LESIONS IN THE B6C3F$_1$/CrlBR MOUSE

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Spontaneous Neoplastic Lesions in the $B6C3F_1$/CrlBR Mouse

February, 1989

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Charles River
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Spontaneous Neoplastic Lesions in the B6C3F$_1$/CrlBR Mouse

INTRODUCTION—The data in these tables were gathered from chronic toxicology studies designed for product registration. All studies were performed in the United States and the United Kingdom at contract toxicology laboratories or pharmaceutical facilities.

I. COMMON STUDY PARAMETERS

Data from 20 groups of control animals are presented in Tables 1 through 20. All studies had the following conditions in common:

- They were 24 months in duration.
- The diet was Purina 5001 Rodent Lab Chow or Purina 5002 Certified Rodent Lab Chow.
- Mice were housed in suspended wire-mesh cages.
- The in-life completion dates of the studies ranged from 1979 to 1986.
- B6C3F$_1$/CrlBR mice were supplied from Charles River production facilities at Wilmington, MA; Portage, MI; Kingston, NY; or from facilities in the United Kingdom.

The encoded study identification (Study ID), the number of mice housed per cage, and the date of terminal sacrifice of the mice in each study group are as follows:

Study ID	#/Cage	Study Dates
A	1	10/80 - 10/82
B	1	10/80 - 10/82
C	1	7/78 - 7/80
D	1	6/82 - 7/84
E	1	6/82 - 7/84
F	3	2/80 - 2/82
G	3	2/80 - 3/82
H	3	3/80 - 3/82
I	3	4/83 - 4/85
J	3	4/83 - 5/85
K	3	12/83 - 12/85
L	1	1/84 - 1/86
M	1	5/82 - 5/84
N	1	3/83 - 4/85
O	1	5/79 - 6/81
P	1	10/78 - 10/80
Q	1	3/82 - 3/84
R	1	2/82 - 3/84
S	1	4/77 - 4/79
T	1	11/82 - 11/84

II. ENVIRONMENTAL CONDITIONS

Environmental conditions for studies are rarely identical even when two studies are conducted in the same facility. Since these studies were conducted in different laboratories, some variation is inherent in the environmental conditions. The range of the mean room temperatures was 68° to 72°F. The range of the mean relative humidity was 45 to 55 percent. Relative humidity control was not precise in all facilities allowing the relative humidity to drop as low as 30 percent in winter months and to rise as high as 75 percent in the summer.

The photoperiod was maintained at a 12-hour light/dark cycle without twilight. Other environmental conditions were either not stated or were inconsistent between facilities. Information on health assessment monitoring other than that associated with pathologic examination conducted in accordance with scheduled or moribund sacrifices was not available.

Overall, environmental conditions were not considered by those performing and interpreting the studies to have affected the outcome of the studies or the distribution of lesions.

III. TABLES 1 AND 10

Tables 1 and 10 provide a summary of neoplastic lesions in male and female B6C3F$_1$/CrlBR mice. Data in these tables are expressed as follows:

Numbers Examined (# Examined)

This column was obtained by combining the total numbers of each tissue/organ examined in the control groups of 20 studies. Tumors of the lymphoreticular system are listed on the basis of the number of *animals* examined since these tumors are frequently found in multiple organs. Data from only 11 studies were included in the lymphoreticular tumor data since the data from the remaining nine studies were not available in a fashion that allowed its incorporation into this data base.

Autolysis of tissue did not routinely exclude samples from inclusion in the data base since some lesions could be diagnosed despite some autolysis. Tissue numbers were adjusted only if the individual study summary indicated that some were missing or that the tissues were inadequate for evaluation.

Number of Lesions (# Lesions)

Entries in this column are the total number of occurrences of this lesion in the tissue/organ or animal (i.e., lymphoreticular system) examined. These values were obtained by summing the number of occurrences in all of the studies used.

Percent

This column represents the mean percent of lesions found in the total population of tissue/organs or animals (i.e., lymphoreticular system) examined. These values were calculated by dividing the total number of lesions by the total number of tissues/organs or animals (i.e., lymphoreticular system) examined and then expressing the result as a percent (i.e., multiplying by 100). The values are expressed to the first decimal place since many values are below 0.5 percent and would be otherwise rounded off to zero.

Range

The range is the highest and lowest percent reported for a given lesion in the individual study groups. For example, in the case of the thyroid gland of male mice, a total of ten follicular cell adenomas was found as primary tumors in 1230 tissues examined, giving a mean of 0.8 percent for the population. In the 20 control groups represented, there was at least one group with no follicular cell adenomas (the low value in the RANGE) and at least one group with as many as 3.6 percent (the high value in the RANGE).

The individual study percentages comprising the range were calculated by dividing the total number of lesions by the total number of tissues/organs or animals (i.e., lymphoreticular system) in each study. Some tissues can be difficult to find in adult animals (e.g., thymus and male mammary gland) unless an obvious lesion exists. It must be remembered that with these tissues the individual group mean percentage may be skewed since the tissue may not have been examined in all animals studied and therefore only those animals with lesions in these tissues may have been recorded.

Expanded Tables for Selected Tissues/Organs (Tables 2-9 and 11-20)

In compiling these tables it became clear that some lesions were diagnosed differently by different pathologists. Some of the lesions included in the tables may not be considered by all pathologists to represent neoplastic changes. For example, benign proliferative lesions in the liver of male B6C3F$_1$/CrlBR mice included nodular hyperplasia, hepatocellular adenoma, and type A hepatocellular nodules. It was not the goal of the present study, however, to define and categorize lesions whose classification could be argued as being neoplastic, non-neoplastic or preneoplastic.

Due to this lack of uniform classification of lesions, it was decided to present a series of tables separating specific diagnoses by study group. This would allow the readers to interpret the data according to their needs. Organ specific lesions summarized in this manner include proliferative lesions of the lymphoreticular system, lung, small intestines, liver, uterus, ovary, pituitary gland, thyroid gland, adrenal gland, and Harderian gland.

IV. SYNONYMOUS TERMS

In general, the diagnoses included in Tables 1 and 10 were the terms also used in the 20 studies in the data base. However, synonymous diagnoses were occasionally encountered in different sets of data. In such cases, the preferred diagnostic term listed in Tables 1 and 10 was substituted for the original term used in the studies. The following table lists these preferred diagnoses that were used in formulating Tables 1 and 10. This tabulated glossary of terms lists the preferred diagnosis under each tissue/organ followed by its synonyms. For example, in the uterus, endometrial stromal polyp was the preferred diagnosis used in Table 10, but the synonymous diagnoses reported in some of the control data included uterine polyp and stromal polyp. The number of tumors reported in Tables 1 and 10 includes all those listed as either the preferred diagnoses or synonymous diagnoses in all 20 studies. In cases where many diagnoses were used to describe a single lesion/tumor, the information was presented in expanded tables in which each diagnosis is separated by study group (see previous explanation).

The following is a listing of preferred and synonymous diagnoses:

GLOSSARY OF SYNONYMS

Skin:

FIBROSARCOMA = subcutaneous fibrosarcoma

Bone:

OSTEOSARCOMA = osteogenic sarcoma

Lung:

ALVEOLAR TYPE II ADENOMA = alveologenic adenoma
ALVEOLAR TYPE II CARCINOMA = alveologenic carcinoma
BRONCHIOLAR/ALVEOLAR ADENOMA = bronchoalveolar lining cell adenoma
BRONCHIOLAR/ALVEOLAR CARCINOMA = bronchiolar/alveolar adenocarcinoma; bronchiolar/alveolar lining cell carcinoma

Stomach:

SQUAMOUS PAPILLOMA, NONGLANDULAR MUCOSA = squamous papilloma; papilloma (nonglandular mucosa)

Liver:

HEPATOCELLULAR ADENOMA = type A hepatocellular nodule
HEPATOCELLULAR CARCINOMA = type B hepatocellular nodule; trabecular carcinoma

Pancreas:

ISLET CELL CARCINOMA = islet cell adenocarcinoma

GLOSSARY OF SYNONYMS

Kidney:

TUBULAR CELL ADENOMA = renal cell adenoma

Testis:

INTERSTITIAL (LEYDIG) CELL TUMOR (Benign) = leydig cell tumor (benign); interstitial cell tumor (benign)

Uterus:

ENDOMETRIAL STROMAL POLYP = uterine polyp; stromal polyp
ENDOMETRIAL STROMAL SARCOMA = endometrial sarcoma; stromal sarcoma
LEIOMYOMA = leiomyoma, muscularis
LEIOMYOSARCOMA = leiomyosarcoma, muscularis

Pituitary Gland:

ADENOMA, ANTERIOR LOBE (Not Otherwise Specified) = tumor, pars anterior (benign)
ADENOMA, PARS DISTALIS = adenoma, anterior (pars distalis)
CARCINOMA, PARS DISTALIS = carcinoma, anterior (pars distalis)
ADENOCARCINOMA, PARS DISTALIS = adenocarcinoma, anterior (pars distalis)

Thyroid Gland:

FOLLICULAR CELL ADENOMA = follicular cell cystadenoma; papillary cystadenoma
FOLLICULAR CELL CARCINOMA = follicular cell adenocarcinoma

Adrenal Gland:

CORTICAL ADENOMA (Not Otherwise Specified) = subcapsular cell adenoma (not otherwise specified)
CORTICAL CARCINOMA (Not Otherwise Specified) = spindle cell tumor (malignant)

Harderian Gland:

CYSTADENOMA = cystadenoma, acini

KEY TO ABBREVIATIONS

The following abbreviations are used in conjunction with many of the tables:

*a = Number of animals examined.

*b = All malignant fibrous histiocytomas listed in the female data, except in the skin, were diagnosed in one study. Individual animal data were not provided; therefore, it could not be determined if all were in the same animal. The two malignant fibrous histiocytomas recorded in the skin were reported in different studies.

NOS = Not otherwise specified.

M = Malignant.

B = Benign.

TABLE 1 (SUMMARY)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
SPONTANEOUS NEOPLASTIC LESIONS
MALE

TOTAL NUMBER OF ANIMALS IN STUDIES: 1363

LOCATION & LESION	# TISSUES EXAM.	# LESIONS	PERCENT	RANGE
HEMATOPOIETIC SYSTEM				
LYMPH NODES	1169			
hemangioma		1	0.1	0- 1.1
THYMUS	934			
fibrosarcoma		1	0.1	0- 3.0
SPLEEN	1270			
hemangioma		8	0.6	0- 3.3
hemangiosarcoma		12	0.9	0- 6.3
angioma		1	0.1	0- 3.3
BONE MARROW	1283			
hemangiosarcoma		1	0.1	0- 1.4
LYMPHORETICULAR TUMORS	832*a			
lymphosarcoma		50	6.0	0-13.5
lymphocytic leukemia		11	1.3	0-18.3
malignant lymphoma, lymphocytic		5	0.6	0- 5.0
malignant lymphoma, lymphoblastic		2	0.2	0- 2.9
malignant lymphoma, mixed cell		5	0.6	0- 7.1
malignant lymphoma, histiocytic		4	0.5	0- 2.9
histiocytic sarcoma		1	0.1	0- 1.4
reticulum cell sarcoma		3	0.4	0- 2.1
INTEGUMENTARY SYSTEM				
SKIN/SUBCUTIS	1292			
squamous cell carcinoma		1	0.1	0- 3.3
dermal polyp		1	0.1	0- 1.6
melanosarcoma		1	0.1	0- 1.2
fibrosarcoma		13	1.0	0-14.8
neurofibrosarcoma		1	0.1	0- 3.3
fibrous histiocytoma (M)		1	0.1	0- 1.4
hemangioma		1	0.1	0- 1.7
hemangiosarcoma		1	0.1	0- 1.6
angiosarcoma		1	0.1	0- 3.3
MAMMARY GLAND	203			
MUSCULOSKELETAL SYSTEM				
SKELETAL MUSCLE	1290			
fibrosarcoma		1	0.1	0- 1.8
BONE	1178			
RESPIRATORY SYSTEM				
TRACHEA	1103			
LUNG	1300			
alveolar type-II adenoma		33	2.5	0-25.4
bronchiolar/alveolar adenoma		108	8.3	0-24.6
adenoma (NOS)		15	1.2	0-13.8
alveolar type-II carcinoma		3	0.2	0- 2.1
bronchiolar/alveolar carcinoma		25	1.9	0- 5.8
adenocarcinoma (NOS)		3	0.2	0- 3.3
CIRCULATORY SYSTEM				
HEART	1299			
hemangiosarcoma		1	0.1	0- 1.4
AORTA	835			
DIGESTIVE SYSTEM				
SALIVARY GLAND	1274			
adenoma (NOS)		1	0.1	0- 1.4
ESOPHAGUS	1112			
squamous papilloma		1	0.1	0- 1.4
STOMACH	1255			
squamous papilloma, nonglandular mucosa		2	0.2	0- 1.4
squamous cell carcinoma (NOS)		3	0.2	0- 1.7
SMALL INTESTINE	1199			
adenoma (NOS)		1	0.1	0- 2.3
adenomatous polyp		1	0.1	0- 1.7
mucosal polyp		1	0.1	0- 1.4
adenocarcinoma (NOS)		5	0.4	0- 2.4
LARGE INTESTINE	1233			
hemangiosarcoma		1	0.1	0- 1.2

TABLE 1 (SUMMARY)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
SPONTANEOUS NEOPLASTIC LESIONS
MALE (Continued)

LOCATION & LESION	# TISSUES EXAM.	# LESIONS	PERCENT	RANGE
LIVER	1294			
nodular hyperplasia		6	0.5	0-20.0
hepatocellular adenoma		222	17.2	0-41.3
hepatocellular carcinoma		171	13.2	4.2-24.6
hepatocellular carcinosarcoma		1	0.1	0- 1.4
hemangioma		9	0.7	0- 3.3
hemangiosarcoma		6	0.5	0- 3.3
GALL BLADDER	855			
PANCREAS (EXOCRINE)	1257			
PANCREAS (ENDOCRINE)	1257			
islet cell adenoma		4	0.3	0- 2.9
URINARY SYSTEM				
KIDNEY	1345			
tubular cell adenoma		2	0.1	0- 1.6
adenocarcinoma, cortex		1	0.1	0- 1.3
URINARY BLADDER	1290			
papillary adenoma		1	0.1	0- 1.1
hemangioma		1	0.1	0- 1.4
REPRODUCTIVE SYSTEM				
TESTIS	1288			
interstitial (Leydig) cell tumor (B)		9	0.7	0- 3.3
hemangiosarcoma		1	0.1	0- 1.0
sarcoma (NOS)		2	0.2	0- 2.9
PROSTATE	1269			
ENDOCRINE SYSTEM				
PITUITARY GLAND	1160			
adenoma, pars intermedia		3	0.3	0- 1.5
adenoma, pars distalis		1	0.1	0- 1.2
adenoma (NOS)		1	0.1	0- 1.3
THYROID GLAND	1230			
follicular cell adenoma		10	0.8	0- 3.6
PARATHYROID GLAND	645			
ADRENAL GLAND	1255			
cortical adenoma (NOS)		5	0.4	0- 2.9
adenoma (NOS)		1	0.1	0- 3.4
pheochromocytoma (B)		2	0.2	0- 3.9
pheochromocytoma (NOS)		1	0.1	0- 1.0
NERVOUS SYSTEM				
BRAIN	1281			
granular cell tumor, meninges (B)		1	0.1	0- 1.3
NERVES	1020			
SPECIAL SENSES				
EYE AND ADNEXA	1240			
cystadenoma, lacrimal gland (NOS)		6	0.5	0- 7.0
HARDERIAN GLAND	1221			
cystadenoma		23	1.9	0-11.3
papillary adenoma		5	0.4	0-10.0
adenoma, accessory gland		4	0.3	0-10.7
adenoma (NOS)		18	1.5	0- 7.1
NASAL TURBINATES	605			

TABLE 2 (EXPANDED)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
LYMPHORETICULAR TUMORS
MALE

STUDY IDENTIFICATION	A	B	L	M	N	O	P	Q	R	S	T
# ANIMALS EXAMINED	80	80	70	60	70	80	86	70	70	96	70
LESION											
lymphosarcoma			5		5	8	6	7	6	13	
%			7.1		7.1	10.0	7.0	10.0	8.6	13.5	
lymphocytic leukemia					11						
%				18.3							
malignant lymphoma, lymphocytic	4	1									
%	5.0	1.3									
malignant lymphoma, lymphoblastic											2
%											2.9
malignant lymphoma, mixed cell											5
%											7.1
malignant lymphoma, histiocytic	2										2
%	2.5										2.9
histiocytic sarcoma				1							
%			1.4								
reticulum cell sarcoma								1		2	
%								1.4		2.1	

TABLE 3 (EXPANDED)
B6C3F_1/CrIBR MICE — 24 MONTHS
LUNG TUMORS
MALE

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
# TISSUES EXAMINED	80	80	113	59	59	30	30	58	30	30	60	70	60	69	80	86	70	70	96	70
LESION																				
alveolar type-II adenoma				12	15														6	
%				20.3	25.4														6.3	
bronchiolar/alveolar adenoma	14	5	1			1	4				11	9	6	17	11	7	6	12		4
%	17.5	6.3	0.9			3.3	13.3				18.3	12.9	10.0	24.6	13.8	7.3	8.6	17.1		5.7
adenoma (NOS)								8	3	4										
%								13.8	10.0	13.3										
alveolar type-II carcinoma					1														2	
%					1.7														2.1	
bronchiolar/alveolar carcinoma	1	3				1					2									4
%	1.3	3.8				3.3					3.3									5.7
bronchioalveolar lining cell carcinoma			1																	
%			0.9																	
bronchiolar/alveolar adenocarcinoma													3	4	2	2	2			
%													5.0	5.8	2.5	2.1	2.9			
adenocarcinoma (NOS)										1								2		
%										3.3								2.9		

TABLE 4 (EXPANDED)
B6C3F_1/CrIBR MICE — 24 MONTHS
SMALL INTESTINAL MASSES
MALE

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
# TISSUES EXAMINED	76	77	66	60	60	30	28	43	24	24	43	70	60	70	80	85	70	70	96	67
LESION																				
adenoma (NOS)								1												
%								2.3												
adenomatous polyp					1															
%					1.7															
mucosal polyp																		1		
%																		1.4		
adenocarcinoma (NOS)				1							1		1			2				
%				1.7							2.3		1.7			2.4				

TABLE 5 (EXPANDED)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
LIVER MASSES
MALE

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
# TISSUES EXAMINED	80	77	98	60	57	30	30	59	30	30	61	70	60	70	80	96	70	70	96	70
LESION																				
nodular hyperplasia						6														
%						20.0														
hepatocellular adenoma	19	15	1	7	4		1	1	1	2	4	16	14	26	33	10	11	20		15
%	23.8	19.5	1.0	11.7	7.0		3.3	1.7	3.3	6.7	6.6	22.9	23.3	37.1	41.3	10.4	15.7	28.6		21.4
hepatocellular nodule, type A																			22	
%																			22.9	
hepatocellular nodule, type B																			4	
%																			4.2	
hepatocellular carcinoma	11	16	6			4	2	8	5	4	15	12	7	12	13	11	5	13		6
%	13.8	20.8	6.1			13.3	6.7	13.6	16.7	13.3	24.6	17.1	11.7	17.1	16.3	11.5	7.1	18.6		8.6
trabecular carcinoma				9	8															
%				15.0	14.0															
hepatocellular carcinosarcoma																		1		
%																		1.4		
hemangioma	1	2		2	1									1			1			1
%	1.3	2.6		3.3	1.8									1.4			1.4			1.4
hemangiosarcoma										1			1				1	1	1	1
%										3.3			1.7				1.4	1.4	1.0	1.4

TABLE 6 (EXPANDED)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
PITUITARY TUMORS
MALE

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
# TISSUES EXAMINED	76	80	65	60	59	26	21	36	27	27	46	69	57	65	75	81	68	64	90	68
LESION																				
adenoma, pars intermedia														1	1		1			
%														1.5	1.3		1.5			
adenoma, pars distalis																1				
%																1.2				
adenoma (NOS)	1																			
%	1.3																			

TABLE 7 (EXPANDED)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
THYROID TUMORS
MALE

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
# TISSUES EXAMINED	78	80	94	58	59	26	28	42	29	28	52	70	60	64	76	86	70	69	91	70
LESION																				
follicular cell adenoma				1			1						1	2	1	1	1		1	
%				1.7			3.6						1.7	3.1	1.3	1.2	1.4		1.1	
follicular cell cystadenoma												1								
%												1.4								

TABLE 8 (EXPANDED)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
ADRENAL TUMORS
MALE

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
# TISSUES EXAMINED	75	79	97	58	58	26	29	50	30	27	60	70	60	68	80	84	69	70	96	69
LESION																				
cortical adenoma (NOS)			1																2	
%			1.0																2.1	
subcapsular cell adenoma (NOS)																				2
%																				2.9
adenoma (NOS)							1													
%							3.4													
pheochromocytoma (B)						1														1
%						3.9														1.5
pheochromocytoma (NOS)			1																	
%			1.0																	

TABLE 9 (EXPANDED)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
HARDERIAN GLAND TUMORS
MALE

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
# TISSUES EXAMINED	76	79	66	60	60	30	28	55	28	28	60	70	50	60	80	86	70	70	95	70
LESION																				
cystadenoma												1		6	9			7		
%												1.4		10.0	11.3			10.0		
*cystadenoma, lacrimal gland (NOS)																6				
%																7.0				
papillary adenoma													5							
%													10.0							
adenoma, accessory gland									1	3										
%									3.6	10.7										
adenoma (NOS)		1		3	2	2											5			5
%		1.3		5.0	3.3	6.7											7.1			7.1

* = Not reported specifically with the Harderian gland data

TABLE 10 (SUMMARY)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
SPONTANEOUS NEOPLASTIC LESIONS
FEMALE

TOTAL # OF ANIMALS IN STUDIES: 1361

LOCATION & LESION	# TISSUES EXAM.	# LESIONS	PERCENT	RANGE
HEMATOPOIETIC SYSTEM				
LYMPH NODES	1168			
hemangiosarcoma		1	0.1	0- 2.0
fibrous histiocytoma (M)		1*b	0.1	0- 3.3
THYMUS	1068			
SPLEEN	1269			
hemangioma		10	0.8	0- 4.3
hemangiosarcoma		5	0.4	0- 2.3
fibrous histiocytoma (M)		1*b	0.1	0- 3.3
BONE MARROW	1282			
LYMPHORETICULAR TUMORS	830*a			
lymphosarcoma		100	12.0	0-28.1
lymphocytic leukemia		12	1.4	0-20.0
malignant lymphoma, lymphocytic		14	1.7	0- 7.5
malignant lymphoma, lymphoblastic		1	0.1	0- 1.5
malignant lymphoma, mixed cell		5	0.6	0- 7.4
malignant lymphoma, histiocytic		12	1.4	0-10.0
histiocytic sarcoma		12	1.4	0- 8.6
reticulum cell sarcoma		2	0.2	0- 2.9
INTEGUMENTARY SYSTEM				
SKIN/SUBCUTIS	1286			
squamous cell papilloma		1	0.1	0- 1.3
sebaceous gland adenoma		1	0.1	0- 1.7
adnexal adenoma (NOS)		1	0.1	0- 3.3
trichoepithelioma		1	0.1	0- 1.1
basal cell carcinoma		1	0.1	0- 1.3
fibroma		1	0.1	0- 1.7
fibrosarcoma		6	0.5	0- 3.3
neurofibrosarcoma		1	0.1	0- 1.3
fibrous histiocytoma (M)		2*b	0.2	0- 3.3
hemangioma		4	0.3	0- 2.9
hemangiosarcoma		3	0.2	0- 3.3
multiple myxosarcoma		1	0.1	0- 1.8
leiomyosarcoma		1	0.1	0- 1.3
sarcoma, undifferentiated		2	0.2	0- 1.4
MAMMARY GLAND	1171			
adenoma (NOS)		5	0.4	0- 7.1
fibroadenoma		4	0.3	0- 2.9
adenocarcinoma (NOS)		10	0.9	0- 3.4
carcinoma (NOS)		7	0.6	0- 5.5
MUSCULOSKELETAL SYSTEM				
SKELETAL MUSCLE	1296			
sarcoma, undifferentiated		1	0.1	0- 1.7
BONE	1175			
osteoma		3	0.3	0- 1.7
osteochondroma		1	0.1	0- 1.7
osteosarcoma		10	0.9	0- 6.7
RESPIRATORY SYSTEM				
NASAL TURBINATES	608			
hemangioma, nasal bones		1	0.2	0- 1.7
TRACHEA	1114			
LUNG	1289			
alveolar type-II adenoma		15	1.2	0-10.9
bronchiolar/alveolar adenoma		43	3.3	0-10.0
adenoma (NOS)		9	0.7	0-10.7
alveolar type-II carcinoma		1	0.1	0- 1.8
bronchiolar/alveolar carcinoma		8	0.6	0- 3.5
adenocarcinoma (NOS)		3	0.2	0- 2.9
CIRCULATORY SYSTEM				
HEART	1296			
AORTA	851			
DIGESTIVE SYSTEM				
SALIVARY GLAND	1270			
adenoma, mucinous		1	0.1	0- 1.7
ESOPHAGUS	1111			
squamous papilloma		1	0.1	0- 1.1

TABLE 10 (SUMMARY)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
SPONTANEOUS NEOPLASTIC LESIONS
FEMALE (Continued)

LOCATION & LESION	# TISSUES EXAM.	# LESIONS	PERCENT	RANGE
STOMACH	1273			
squamous papilloma, nonglandular mucosa		6	0.5	0- 4.3
squamous papilloma, inverted		1	0.1	0- 1.1
gastric adenoma		1	0.1	0- 1.1
gastric carcinoma		1	0.1	0- 1.1
squamous cell carcinoma, in situ		1	0.1	0- 1.3
squamous cell carcinoma, nonglandular mucosa		1	0.1	0- 1.3
fibrous histiocytoma (M)		1*b	0.1	0- 3.3
mast cell tumor		1	0.1	0- 1.4
SMALL INTESTINE	1246			
adenoma (NOS)		2	0.2	0- 2.4
adenomatous polyp		1	0.1	0- 1.4
LARGE INTESTINE	1259			
fibrous histiocytoma (M)		1*b	0.1	0- 3.3
LIVER	1279			
nodular hyperplasia		1	0.1	0- 3.6
hepatocellular adenoma		91	7.1	0-17.1
hepatocellular carcinoma		31	2.4	0- 6.3
hemangioma		4	0.3	0- 2.9
hemangiosarcoma		1	0.1	0- 1.4
Kupffer cell sarcoma		1	0.1	0- 0.9
GALL BLADDER	888			
PANCREAS (EXOCRINE)	1265			
fibrous histiocytoma (M)		1*b	0.1	0- 3.4
fibrosarcoma		1	0.1	0- 3.6
PANCREAS (ENDOCRINE)	1265			
islet cell adenoma		4	0.3	0- 2.5
islet cell carcinoma		4	0.3	0- 3.5
URINARY SYSTEM				
KIDNEY	1326			
URINARY BLADDER	1278			
REPRODUCTIVE SYSTEM				
UTERUS	1279			
endometrial stromal polyp		37	2.9	0-10.0
papillary cystadenoma		1	0.1	0-18.2
adenoma (NOS)		1	0.1	0- 1.3
carcinoma (NOS)		1	0.1	0- 1.3
adenocarcinoma (NOS)		8	0.6	0- 3.5
fibroma		2	0.2	0- 1.7
fibrosarcoma		2	0.2	0- 1.1
endometrial stromal sarcoma		8	0.6	0- 3.5
leiomyoma		5	0.4	0- 3.5
leiomyosarcoma		4	0.3	0- 3.4
hemangioma		11	0.9	0- 5.0
hemangiosarcoma		1	0.1	0- 1.4
angiosarcoma		1	0.1	0- 3.4
sarcoma, undifferentiated		1	0.1	0- 3.4
OVARY	1235			
cystadenoma		4	0.3	0- 2.2
papillary cystadenoma		3	0.2	0- 3.6
papillary adenoma		2	0.2	0- 2.2
adenoma (NOS)		1	0.1	0- 1.3
tubular carcinoma		1	0.1	0- 1.4
adenocarcinoma (NOS)		1	0.1	0- 1.8
luteoma		3	0.2	0- 1.5
granulosa theca cell tumor (B)		7	0.6	0- 3.7
granulosa cell tumor (M)		2	0.2	0- 2.0
teratoma (B)		2	0.2	0- 3.7
hemangioma		10	0.8	0- 4.3
hemangiosarcoma		1	0.1	0- 1.7
ENDOCRINE SYSTEM				
PITUITARY GLAND	1184			
adenoma, pars intermedia		5	0.4	0- 4.2
adenoma, pars distalis		94	7.9	0-29.0
adenoma, anterior lobe (NOS)		14	1.2	0-11.7
adenoma (NOS)		63	5.3	0-25.6
craniopharyngioma		1	0.1	0- 1.3
carcinoma, pars distalis		3	0.3	0- 2.8
adenocarcinoma, pars distalis		2	0.2	0- 1.4
adenocarcinoma (NOS)		1	0.1	0- 1.3

TABLE 10 (SUMMARY)
B6C3F$_1$/CrIBR MICE — 24 MONTHS
SPONTANEOUS NEOPLASTIC LESIONS
FEMALE (Continued)

LOCATION & LESION	# TISSUES EXAM.	# LESIONS	PERCENT	RANGE
THYROID GLAND	1239			
follicular cell adenoma		30	2.4	0-10.0
follicular cell carcinoma		5	0.4	0- 3.2
adenocarcinoma (NOS)		1	0.1	0- 1.3
PARATHYROID GLAND	656			
adenoma		1	0.2	0- 1.6
ADRENAL GLAND	1267			
cortical adenoma (NOS)		4	0.3	0- 2.7
cortical carcinoma (NOS)		3	0.2	0- 1.4
pheochromocytoma (B)		4	0.3	0- 2.6
pheochromocytoma (M)		1	0.1	0- 1.3
pheochromocytoma (NOS)		3	0.2	0- 2.7
NERVOUS SYSTEM				
BRAIN	1294			
NERVES	1034			
SPECIAL SENSES				
EYE AND ADNEXA	1271			
adenoma, accessory gland		2	0.2	0- 3.4
cystadenoma, lacrimal duct		4	0.3	0- 4.7
HARDERIAN GLAND	1251			
cystadenoma		20	1.6	0- 8.6
papillary cystadenoma		1	0.1	0- 1.8
papillary adenoma		6	0.5	0- 8.0
adenoma (NOS)		8	0.6	0- 4.3
adenocarcinoma (NOS)		1	0.1	0- 1.4

TABLE 11 (EXPANDED)
B6C3F$_1$/CrIBR MICE — 24 MONTHS
LYMPHORETICULAR TUMORS
FEMALE

STUDY IDENTIFICATION	A	B	L	M	N	O	P	Q	R	S	T
# ANIMALS EXAMINED	80	80	70	60	70	80	86	70	70	96	68
LESION											
lymphosarcoma			4	1	10	17	19	13	9	27	
%			5.7	1.6	14.3	21.3	22.0	18.6	12.9	28.1	
lymphocytic leukemia				12							
%				20.0							
malignant lymphoma, lymphocytic	6	4									4
%	7.5	5.0									5.9
malignant lymphoma, lymphoblastic											1
%											1.5
malignant lymphoma, mixed cell											5
%											7.4
malignant lymphoma, histiocytic	8	4									
%	10.0	5.0									
histiocytic sarcoma			6	2	2					1	1
%			8.6	3.3	2.9					1.0	1.5
reticulum cell sarcoma								2			
%								2.9			

TABLE 12 (EXPANDED)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
LUNG TUMORS
FEMALE

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
# TISSUES EXAMINED	80	79	115	55	56	29	30	56	29	30	58	70	60	70	80	86	70	70	96	70
LESION																				
alveolar type-II adenoma				6	5														4	
%				10.9	8.9														4.2	
bronchiolar/alveolar adenoma	2		1			1	1				3	4	3	5	3	8	7	3		2
%	2.5		0.9			3.5	3.3				5.2	5.7	5.0	7.1	3.8	9.3	10.0	4.3		2.9
bronchoalveolar lining cell adenoma			2																	
%			1.7																	
adenoma (NOS)								6	1	2										
%								10.7	3.4	6.7										
alveolar type-II carcinoma					1															
%					1.8															
bronchiolar/alveolar carcinoma	1	1				1														1
%	1.3	1.3				3.5														1.4
bronchiolar/alveolar adenocarcinoma													2		1		1			
%													3.3		1.3		1.4			
adenocarcinoma (NOS)														1				2		
%														1.4				2.9		

TABLE 13 (EXPANDED)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
SMALL INTESTINAL MASSES
FEMALE

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
# TISSUES EXAMINED	76	77	99	60	59	29	30	53	21	22	52	70	60	70	80	85	70	70	94	69
LESION																				
adenoma (NOS)																2				
%																2.4				
adenomatous polyp																				1
%																				1.4

TABLE 14 (EXPANDED)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
LIVER MASSES
FEMALE

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
# TISSUES EXAMINED	80	80	107	47	55	28	30	57	29	28	57	70	60	70	80	95	70	70	96	70
LESION																				
nodular hyperplasia						1														
%						3.6														
hepatocellular adenoma	1		3	5	1					1		9	9	12	12	11	6	11		4
%	1.3		2.8	10.6	1.8					3.6		12.9	15.0	17.1	15.0	11.6	8.6	15.7		5.7
hepatocellular nodule, type A																			6	
%																			6.3	
hepatocellular nodule, type B																			2	
%																			2.1	
hepatocellular carcinoma	4		3					1			1	1	1	4	5		1	3		2
%	5.0		2.8					1.8			1.8	1.4	1.7	5.7	6.3		1.4	4.3		2.9
trabecular carcinoma				2	1															
%				4.3	1.8															
hemangioma		1											1	2						
%		1.3											1.7	2.9						
hemangiosarcoma														1						
%														1.4						
Kupffer cell sarcoma			1																	
%			0.9																	

TABLE 15 (EXPANDED)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
UTERINE MASSES
FEMALE

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
# TISSUES EXAMINED	79	79	111	57	57	29	30	55	28	29	54	70	60	70	80	86	70	70	95	70
LESION																				
endometrial stromal polyp			1								1	3	6		3	7	3	5		
%			0.9								1.9	4.3	10.0		3.8	8.1	4.3	7.1		
stromal polyp																			3	
%																			3.2	
uterine polyp		1																	4	
%		1.3																	4.2	
papillary cystadenoma								1												
%								1.8												
adenoma (NOS)		1																		
%		1.3																		
carcinoma (NOS)	1																			
%	1.3																			
adenocarcinoma (NOS)				2								1				3	1	1		
%				3.5								1.4				3.5	1.4	1.4		
fibroma		1											1							
%		1.3											1.7							
fibrosarcoma			1																1	
%			0.9																1.1	
endometrial stromal sarcoma				1	2															
%				1.8	3.5															
endometrial sarcoma																			1	
%																			1.1	
stromal sarcoma														1	1				2	
%														1.4	1.3				2.1	
leiomyoma					2								1							
%					3.5								1.7							
leiomyoma, muscularis															2					
%															2.5					
leiomyosarcoma				1						1								1		
%				1.8						3.4								1.4		
leiomyosarcoma, muscularis															1					
%															1.3					
hemangioma			1										3	2	1	1		2	1	
%			0.9										5.0	2.9	1.3	1.2		2.9	1.1	
hemangiosarcoma																				1
%																				1.4
angiosarcoma						1														
%						3.4														
sarcoma, undifferentiated										1										
%										3.4										

TABLE 16 (EXPANDED)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
OVARIAN TUMORS
FEMALE

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
# TISSUES EXAMINED	79	79	108	52	55	27	28	53	27	27	51	69	60	68	73	82	69	69	89	70
LESION																				
cystadenoma														1		1			2	
%														1.5		1.2			2.2	
papillary cystadenoma			1				1				1									
%			0.9				3.6				2.0									
papillary adenoma																			2	
%																			2.2	
adenoma (NOS)	1																			
%	1.3																			
tubular carcinoma												1								
%												1.4								
adenocarcinoma (NOS)					1															
%					1.8															
luteoma												1		1				1		
%												1.4		1.5				1.5		
granulosa theca cell tumor (B)				1						1	1	1			1	1	1			
%				1.9						3.7	2.0	1.4			1.4	1.2	1.4			
granulosa cell tumor (M)								1			1									
%								1.9			2.0									
teratoma (B)									1							1				
%									3.7							1.2				
hemangioma			1		1							3	1	1					2	1
%			0.9		1.8							4.3	1.7	1.5					2.2	1.4
hemangiosarcoma													1							
%													1.7							

TABLE 17 (EXPANDED)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
PITUITARY TUMORS
FEMALE

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
# TISSUES EXAMINED	80	78	83	56	60	24	28	47	27	28	53	69	54	70	72	79	67	69	75	65
LESION																				
adenoma, pars intermedia															3			2		
%															4.2			2.9		
adenoma, pars distalis			1									6	12	9	13	14	19	20		
%			1.2									8.7	22.2	12.9	18.0	18.0	28.4	29.0		
adenoma, anterior lobe (NOS)				4	7						3									
%				7.1	11.7						5.7									
adenoma (NOS)	12	20					1	3	4	3									15	5
%	15.0	25.6					3.6	6.4	14.8	10.7									20.0	7.7
craniopharyngioma	1																			
%	1.3																			
carcinoma, pars distalis													1		2					
%													1.9		2.8					
adenocarcinoma, pars distalis												1				1				
%												1.4				1.3				
adenocarcinoma (NOS)																			1	
%																			1.3	

TABLE 18 (EXPANDED)
B6C3F$_1$/CrlBR MICE — 24 MONTHS
THYROID TUMORS
FEMALE

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
# TISSUES EXAMINED	77	75	99	58	60	27	26	47	28	26	54	69	60	68	78	85	70	70	93	69
LESION																				
follicular cell adenoma		2			1	1							6	1	2	4		5	2	3
%		2.7			1.7	3.7							10.0	1.5	2.6	4.7		7.1	2.2	4.3
follicular cell cystadenoma												1								
%												1.4								
papillary cystadenoma			2																	
%			2.0																	
follicular cell carcinoma			1																	
%			1.0																	
follicular cell adenocarcinoma														1					3	
%														1.5					3.2	
adenocarcinoma (NOS)		1																		
%		1.3																		

TABLE 19
B6C3F$_1$/CrlBR MICE — 24 MONTHS
ADRENAL TUMORS
FEMALE

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
# TISSUES EXAMINED	80	78	110	56	54	28	28	51	29	29	57	70	60	70	79	85	70	70	94	69
LESION																				
cortical adenoma (NOS)			3													1				
%			2.7													1.2				
spindle cell tumor (M)												1								
%												1.4								
cortical carcinoma (NOS)	1	1																		
%	1.3	1.3																		
pheochromocytoma (B)		2									1				1					
%		2.6									1.8				1.3					
pheochromocytoma (M)															1					
%															1.3					
pheochromocytoma (NOS)			3																	
%			2.7																	

TABLE 20
B6C3F$_1$/CrlBR MICE — 24 MONTHS
HARDERIAN GLAND TUMORS
FEMALE

STUDY IDENTIFICATION	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
# TISSUES EXAMINED	79	79	95	59	60	29	30	54	29	28	57	70	50	60	80	86	70	70	96	70
LESION																				
cystadenoma												6		4	3			6	1	
%												8.6		6.7	3.8			8.6	1.0	
papillary cystadenoma											1									
%											1.8									
papillary adenoma													4						2	
%													8.0						2.1	
*adenoma, accessory gland							1		1											
%							3.3		3.4											
adenoma (NOS)		1					1				1						2			3
%		1.3					3.3				1.8						2.9			4.3
adenocarcinoma (NOS)																		1		
%																		1.4		

* = Not reported specifically with the Harderian gland data

APPENDIX 6

QUANTITATIVE DOSE-RESPONSE ASSESSMENT FOR TOXAPHENE

APPENDIX 6:

TOXAPHENE
QUANTITATIVE DOSE-RESPONSE ASSESSMENT

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TOXAPHENE
Quantitative Dose-Response Assessment

1. Dose-Response Data

Although Hercules strongly believes that the dose-response relationship for toxaphene is nonlinear and that a margin-of-exposure assessment is most appropriate for toxaphene, the cancer potency corresponding to a low-dose linear dose-response relationship is characterized, and the maximum likelihood estimate (q_1) of the low-dose slope is quantified as well as the corresponding upper bound (q_1^*) on the cancer potency. In addition, in order to support a margin-of-exposure assessment for toxaphene, the dose-response data on liver tumors in mice have been used to determine the maximum likelihood estimate of the ED_{10} (the effective dose corresponding to an increase of 0.10 in the probability of an adverse response) and a corresponding LED_{10} (a 95% lower confidence limit or other lower bound on the ED_{10}).

The NCI toxaphene mouse oncogenicity study (1979) is used to characterize the cancer dose-response relationship in mice. The liver tumor incidence in this study is analyzed using the pathology working group (PWG) findings (Environmental Pathology Laboratories, Inc., 1996). Table 1 contains summaries of the corresponding cumulative response frequencies. Supplemental Table 1 at the end of this appendix contains the more detailed raw data. These data are indicated separately for male and female mice and for each dose group include the animal number, the animal's observation time, the presence or absence of a liver adenoma (originally a "neoplastic nodule"), the presence or absence of a liver carcinoma, the presence or absence of a liver tumor (adenoma or carcinoma), and whether or not the animal was autolytic at the observation time.

Table 1. Summaries of the cumulative liver tumor response frequencies in the NCI toxaphene mouse oncogenicity study (1979) based on the pathology working group (PWG) findings

Adenoma and/or Carcinoma			
Male		Female	
Dose: mg/kg/day (time-weighted average)	# Tumor Bearing / # at Risk	Dose: mg/kg/day (time-weighted average)	# Tumor Bearing / # at Risk
0	2/10	0	0/10
13.055	37/50	14.85	11/49
26.110	45/47	29.70	39/47

2. Liver Adenoma and/or Carcinoma Data

Table 2 indicates the dose-response characteristics (ED_{10}, LED_{10}, q_1, and q_1^*) based on the liver adenoma and/or carcinoma data. When the time the mouse is observed is ignored, the dose-response modeling is based on the multistage model's best estimates (ED_{10} and q_1) and linearized multistage model's bounds (LED_{10} and q_1^*). When the time of the observation is not ignored but included, the dose-response characteristics (ED_{10}, LED_{10}, q_1, and q_1^*) are based on the multistage-Weibull model version of the Armitage-Doll model (Armitage and Doll, 1961). The latter case in which the time of the observation is not ignored is more scientifically defensible. Each of the dose-response characteristics (ED_{10}, LED_{10}, q_1, and q_1^*) are presented separately for male and female mice and then presented as the geometric mean of the male and female values.

When the time of the observation is included and the Multistage-Weibull model is used, the low-dose slope of the added risk per mg/kg/day can be either estimated directly at a low dose corresponding to an upper bound on potential human exposures (e.g., 1×10^{-6} mg/kg/day) or characterized by an upper bound based on a linear extrapolation below a benchmark dose (e.g., ED_{10} or its lower bound, the LED_{10}). The quantitative results from both procedures are tabled in this Appendix. However, the latter procedure is more conservative in that the assumption of a linear dose-response relationship below the benchmark dose provides an upper bound on predicted risks at potential human exposures. The potential human exposures are far below the observed experimental dose levels (e.g., 1×10^{-6} mg/kg/day is more than 10 million fold smaller than the nonzero experimental dose levels, approximately 13 and 26 mg/kg/day). The results of the more conservative procedure using a benchmark dose (e.g., ED_{10} or LED_{10}) which is much closer to the observed experimental data are emphasized.

Including the data on the time of observation, the conservative low-dose linear extrapolation below the benchmark dose, and the current default procedures for interspecies extrapolation between mice and humans, the best estimates of the dose-response characteristics in Table 2 are

ED_{10} = 4.93 mg/kg/day in mice
-- geometric mean between males and females

q_1 = 0.14 extra risk per mg/kg/day in humans
-- geometric mean between males and females

ED_{10} = 3.57 mg/kg/day in mice
-- worst case between males and females

q_1 = 0.19 extra risk per mg/kg/day in humans
-- worst case between males and females

and the corresponding bounds are

LED_{10} = 4.19 mg/kg/day in mice
-- geometric mean between males and females

q_1^* = 0.16 extra risk per mg/kg/day in humans
-- geometric mean between males and females

LED_{10} = 2.87 mg/kg/day in mice
-- worst case between males and females

q_1^* = 0.23 extra risk per mg/kg/day in humans
-- worst case between males and females.

Table 2. Dose-response characteristics (ED_{10}, LED_{10}, q_1, and q_1^*) based on the liver adenoma and/or carcinoma incidence data in the NCI toxaphene mouse oncogenicity study (1979) and the pathology working group (PWG) findings: extra risks

Liver Adenoma and/or Carcinoma Data in Mice	Maximum Likelihood Estimates		Bounds: 95% Confidence Limits	
	ED_{10} mg/kg/day in mice	Slope (q_1) per mg/kg/day in humans Slope (q_1) to Extra Risk at 1 x 10^{-6} mg/kg/day Slope (q_1) to Extra Risk at ED_{10}	LED_{10} mg/kg/day in mice: Lower Bound on ED_{10}	Upper Bound on Slope (q_1^*) per mg/kg/day in humans Slope (q_1^*) to Extra Risk at 1 x 10^{-6} mg/kg/day Slope (q_1^*) to Extra Risk at LED_{10}
Interspecies extrapolation of cancer potency from mice to humans based on default assumption of interspecies equivalence on the (body weight)$^{3/4}$ scale but NOT Adjusted for Interspecies Differences in Background Transition Rates				
Including Data on Observation Time				
Male	3.57	3.7 x 10^{-7} 0.19	2.87	5.7 x 10^{-7} 0.23
Female	6.81	1.0 x 10^{-7} 0.098	6.11	1.3 x 10^{-7} 0.11
Geometric Mean[1]	4.93	1.9 x 10^{-7} 0.14	4.19	2.7 x 10^{-7} 0.16
Excluding Data on Observation Time				
Male	1.67	0.40	0.86	0.82
Female	6.07	1.9 x 10^{-8}	4.33	0.10
Geometric Mean	3.18	8.7 x 10^{-5}	1.93	0.29

[1] The geometric mean of the male and female values is the square root of the product of the male and female values; for example, the geometric mean for the ED_{10} is $4.93 = (3.57 \times 6.81)^{0.5}$.

Details of the Statistical Dose-Response Modeling

Some of the technical details of the statistical dose-response modeling methodology used for Table 2 and other similar tables in this appendix are as follows.

When the data on the observation times is excluded and the multistage and linearized multistage models are fit to the data, the calculated values (ED_{10}, LED_{10}, q_1, and q_1^*) are determined using EPA's own GLOBAL software (originally written for EPA by K. S. Crump, Inc.). These numbers have been double checked using the more extensive general purpose software GEN.T (written by Sielken, Inc.). Both software yield comparable results when calculating comparable quantities.

The q_1^* value is an upper bound on the rate of increase in the cancer probability. GLOBAL and GEN.T can both calculate not only the upper bounds on the cancer probability (in mice) as a function of dose -- the q_1^* value is basically the slope of the 95% upper confidence limits (UCLs) in the low-dose region -- but also the multistage model and q_1 value that best fits the mouse data -- the maximum likelihood estimate (MLE). The calculated q_1 value in Table 2 (and analogous values in other tables) is a best estimate -- a maximum likelihood estimate (MLE) -- and is not a lower bound, although the MLE is frequently misrepresented or misinterpreted as a lower bound. GEN.T (but not GLOBAL) can calculate actual lower bounds on the cancer probability (in mice) as a function of dose -- a 95% lower confidence limit (LCL). Thus, GEN.T calculates lower bounds as well as best estimates and upper bounds. GEN.T calculates the lower bounds associated with the multistage model using the same statistical method used in the linearized multistage model tc calculate upper bounds.

The MLE for q_1 is the best estimate of the low-dose slope (the approximate rate of increase in the cancer probability at low doses), the q_1^* value implies an upper bound on how much bigger the slope might be, and the lower bounds imply how small the slope might be. If the lower bound on the slope is negative, then there is sufficient experimental variability in the data to not reject the hypothesis that the cancer probability does not increase at low doses.

Similarly, the LED_{10} value is a lower bound on the dose corresponding to an increase of 0.10 in the cancer probability above the background level. GLOBAL and GEN.T can both calculate not only the lower bounds on the dose (in mice) -- the LED_{10} value is basically a 95% lower confidence limit (LCL) -- but also the multistage model and ED_{10} value that best fits the mouse data -- the maximum likelihood estimate (MLE). The calculated ED_{10} value in Table 2 (and analogous values in other tables) is a best estimate -- a maximum likelihood estimate (MLE) -- and is not an upper bound on the dose corresponding to an increase of 0.10 in the cancer probability above the background level, although the ED_{10} (i.e., the MLE) is frequently misrepresented or misinterpreted as an upper bound on the dose corresponding to an increase of 0.10 in the cancer probability above the background level. GEN.T (but not GLOBAL) can calculate actual upper bounds on the dose corresponding to an increase of 0.10 in the cancer probability (in mice) above the background level (in mice) -- the 95% upper confidence limit (UCL). Thus, GEN.T calculates upper bounds on target doses as well as best estimates of target doses and lower bounds on target doses. GEN.T calculates the upper bounds on target doses associated with the multistage model using the same statistical method used in the linearized multistage model to calculate lower bounds on target doses.

The GEN.T software generates the bounds which are not available from the GLOBAL software.

Using GEN.T, the lower bounds on the slope of the cancer probability in the low-dose region were calculated. They were frequently negative for the toxaphene data. This supports the hypothesis that toxaphene may not increase the cancer probability at low doses. Because there were only three dose levels (the control level and two treatment levels), both the upper bounds (q_1^*) and the corresponding lower bounds reflect a lot of uncertainty. Although the lower bounds have as much experimental support as the upper bounds, only the upper bounds are reported in this appendix.

The q_1^* calculations in Table 2 are consistent with the usual EPA default procedures. In particular, the parameters in the multistage and linearized multistage models have been restricted to be positive (i.e., non-negative) which forces the fitted dose-response model to be increasing (i.e., non-decreasing) at all dose levels. This default assumption has been used although there is not experimental evidence available to indicate that this conservative default assumption is necessarily appropriate for toxaphene.

The EPA usually chooses the maximum or geometric mean of the male and female based numbers to characterize the cancer potency and chooses the minimum or geometric mean of the male and female based numbers to characterize the dose corresponding to a 10% increase in the cancer probability above the background cancer probability. This practice is followed in the summary characterizations.

The q_1^* value should be interpreted as an upper bound on the rate (per mg/kg/day) of increase in the human lifetime cancer probability above the background lifetime cancer probability. Thus, if a human's lifetime average daily dose were to increase by 1 mg/kg/day, then the human's lifetime cancer probability would increase by the q_1^* value. Similarly, if a human's lifetime average daily dose were to increase by 0.1 mg/kg/day, then the human's cancer probability would increase by 0.1 times the q_1^* value. The increases in probability are the increases in the lifetime cancer probability and not the increase per year, or any such thing.

When the data on the observation times is included and the multistage-Weibull models are fit to the data, the calculated values (ED_{10}, LED_{10}, q_1, and q_1^*) are determined using the more general purpose software GEN.T (written by Sielken, Inc.). The models are fit using the maximum likelihood estimation criterion. In accord with EPA's conservative (health protective) default assumption, the parameters in the models are restricted to be positive (i.e., non-negative). The upper and lower bounds are generated using a nonparametric bootstrap procedure. From a sample of 100 bootstrap values, the upper bound is calculated as the sample value such that 95% of the sample is less than or equal to that sample value, and, analogously, the lower bound is calculated as the sample value such that 95% of the sample is greater than or equal to that sample value.

Interspecies Extrapolation

The current default assumption for the interspecies extrapolation of the cancer potency (q_1 or q_1^*) from animals to humans is to assume that the species will respond equivalently if exposed to the same dose on the mg/(kg)$^{3/4}$/day scale; that is, interspecies equivalence on the (body weight)$^{3/4}$ scale.

The current default method of interspecies extrapolation incorporates simplified assumptions and approximations that fail to properly assess the impact of quantitative differences in human and experimental animal background transition rates from stage to stage in the multistage carcinogenic process (Sielken and Stevenson, 1994). The dependence of the cancer potency (q_1 or q_1^*) on the background transition rates is intuitive in the following sense. In the multistage theory of cancer, the probability of a tumor depends on the product of the transition rates from stage to stage. When there is a dose-dependent increase in one of these transition rates, the absolute magnitude of the increase in product (and hence the tumor probability) depends on the magnitudes of the other transition rates. Thus, the magnitude of the increase in the tumor probability and the cancer potency (q_1 or q_1^*) associated with a dose-dependent increase in a transition rate depends on the magnitudes of the other transition rates.

For example, if the background transition rates are small, then a specified increase in a dose-dependent transition rate results in a smaller change (absolute change not proportional change) in the product than would occur if the background transition rates were larger. For instance, if there were three transition rates and each one was 0.01, then the product would be 0.000001, and a dose-related increase in one of the transition rates from 0.01 to 0.05 (an increase of 0.04) would increase the product to 0.000005 (an increase of 0.000004). However, if the three background transition rates were each 0.1, then the product would be 0.001, and a dose-related increase in one of the transition rates from 0.1 to 0.14 (an increase of 0.04) would increase the product to 0.00014 (an increase of 0.0004). In terms of absolute magnitude (as opposed to relative magnitude or proportional change), an increase of 0.000004 is 100 fold smaller than an increase of 0.0004.

Following Sielken and Stevenson (1994), an approximate adjustment to the current default method of interspecies extrapolation for the interspecies differences in background transition rates is

$$q_1(\text{Adjusted}) = q_1(\text{Unadjusted}) \times [\ P_{\text{Human}}(0) \ / \ P_{\text{Mice}}(0)\ ]^{(k-1)/k}$$

when the bioassay results for mice are to be extrapolated to humans and

$P_{\text{Human}}(0)$ = background tumor probability in humans,

$P_{\text{Mice}}(0)$ = background tumor probability in mice, and

k = the number of transition rates.

Similarly, for the linearized multistage model upper bounds on the cancer potency

$$q_1^*(\text{Adjusted}) = q_1^*(\text{Unadjusted}) \times [\ P_{\text{Human}}(0) \ / \ P_{\text{Mice}}(0)\ ]^{(k-1)/k}.$$

A simplified derivation of this adjustment is given in Section 4 of this appendix.

According to the American Cancer Society (1996), for humans

$P_{\text{Human}}(0)$ = Background liver tumor probability in males = 0.000055 and

$P_{\text{Human}}(0)$ = Background liver tumor probability in females = 0.000030.

According to Charles River (1989), for B6C3F1 mice

$P_{\text{Mice}}(0)$ = Background liver adenoma and/or carcinoma probability in males = 0.304 and

$P_{Mice}(0)$ = Background liver adenoma and/or carcinoma probability in females = 0.095.

Therefore, even if there are only two stages (k=2) in the multistage carcinogenic process, the multiplicative adjustment of the current default method of interspecies extrapolation for the interspecies differences in background transition rates is

$$[\ P_{Human}(0)\ /\ P_{Mice}(0)\ ]^{(k-1)/k} = [\ 0.000055\ /\ 0.304\ ]^{(2-1)/2} = 0.0135$$

for male B6C3F1 mice and

$$[\ P_{Human}(0)\ /\ P_{Mice}(0)\ ]^{(k-1)/k} = [\ 0.000030\ /\ 0.095\ ]^{(2-1)/2} = 0.018$$

for female B6C3F1 mice. These multiplicative adjustments to the extrapolated cancer potency (q_1 or q_1^*) correspond to approximately a 70 fold decrease in the cancer potency extrapolated from male B6C3F1 mice and approximately a 60 fold decrease in the cancer potency extrapolated from female B6C3F1 mice.

If there were more than two stages, then the adjustment multiplier and corresponding adjusted values of the cancer potency would be even smaller and the decreases in the extrapolated cancer potencies even greater. For example, if k=3, then the adjustment multiplier for male B6C3F1 mice would decrease from 0.0135 to 0.0032 and the adjustment multiplier for female B6C3F1 mice would decrease from 0.018 to 0.0046. Thus, if k=3, the multiplicative adjustments to the extrapolated cancer potency (q_1 or q_1^*) correspond to approximately a 300 fold decrease in the human cancer potency extrapolated from male B6C3F1 mice and approximately a 200 fold decrease in the human cancer potency extrapolated from female B6C3F1 mice.

In Table 2, EPA's default assumptions were followed and no adjustments were made for the interspecies differences in the background transition rates. However, the cancer potency characterizations (q_1 and q_1^*) in Table 3 indicate the quantitative impact of making even a minimal adjustment for the interspecies differences in the background transition rates. That is, in Table 3 it is only assumed that there are two stages in the multistage carcinogenic process for toxaphene. If more than two stages had been assumed, then the cancer potency characterizations (q_1 and q_1^*) would have been further decreased.

Table 3. Dose-response characteristics (ED_{10}, LED_{10}, q_1, and q_1^*) based on the liver adenoma and/or carcinoma incidence data in the NCI toxaphene mouse oncogenicity study (1979) and the pathology working group (PWG) findings: extra risks with and without minimal adjustments for interspecies differences in background transition rates

Liver Adenoma and/or Carcinoma Data in Mice	Maximum Likelihood Estimates		Bounds: 95% Confidence Limits	
	ED_{10} mg/kg/day in mice	Slope (q_1) per mg/kg/day in humans[1] Slope (q_1) to Extra Risk at 1 x 10^{-6} mg/kg/day Slope (q_1) to Extra Risk at ED_{10}	LED_{10} mg/kg/day in mice: Lower Bound on ED_{10}	Upper Bound on Slope (q_1^*) per mg/kg/day in humans[1] Slope (q_1^*) to Extra Risk at 1 x 10^{-6} mg/kg/day Slope (q_1^*) to Extra Risk at LED_{10}
Minimal Adjustment for Interspecies Differences in Background Transition Rates				
Including Data on Observation Time				
Male	3.57	5.0 x 10^{-9} 0.0026	2.87	7.7 x 10^{-9} 0.0031
Female	6.81	1.8 x 10^{-9} 0.0018	6.11	2.3 x 10^{-9} 0.0020
Excluding Data on Observation Time				
Male	1.67	0.0054	0.86	0.011
Female	6.07	3.4 x 10^{-10}	4.33	0.0018
NOT Adjusted for Interspecies Differences in Background Transition Rates				
Including Data on Observation Time				
Male	3.57	3.7 x 10^{-7} 0.19	2.87	5.7 x 10^{-7} 0.23
Female	6.81	1.0 x 10^{-7} 0.098	6.11	1.3 x 10^{-7} 0.11
Excluding Data on Observation Time				
Male	1.67	0.40	0.86	0.82
Female	6.07	1.9 x 10^{-8}	4.33	0.10

[1] Interspecies extrapolation of cancer potency from mice to humans based on default assumption of interspecies equivalence on the (body weight)$^{3/4}$ scale

Extra Risks versus Added Risks

Although the EPA default practice has been to quantify dose-response characteristics such as the ED_{10}, LED_{10}, q_1, and q_1^* in terms of the extra risk instead of added risk, there are important advantages to using added risk instead of extra risks.

If the dose-response characteristic is defined in terms of added risk, then the dose-response characteristic refers to the whole population. This makes the communication of dose-response characteristics based on added risk more straightforward and the relevant population clearer. Furthermore, if two different substances have the same added risk and the same number of individuals are exposed to each substance, then the increased number of individuals expected to develop the specified adverse health effect are the same for both substances. On the other hand, if the dose-response characteristic is defined in terms of extra risk, then the dose-response characteristic only refers to part of the population (a subset of the population) and not necessarily the whole population. This makes the communication of dose-response characteristics based on extra risk less straightforward and the relevant population less clear. Furthermore, if two different substances have the same extra risk and the same number of individuals are exposed to each substance, then the increased number of individuals expected to develop the specified adverse health effect is not necessarily the same for both substances.

If

P(d) = Probability of an adverse health effect when the dose is d,

then the added risk at dose d is defined as

$$\text{Added Risk (d)} = P(d) - P(0)$$

which is simply the increase in the probability at dose d above the background probability at dose 0. On the other hand, the extra risk at dose d is defined as

$$\begin{aligned}\text{Extra Risk (d)} &= [\ \text{Added Risk (d)}\ ]\ /\ [\ 1 - P(0)\ ]\\ &= [\ P(d) - P(0)\ ]\ /\ [\ 1 - P(0)\ ]\end{aligned}$$

which is the increase in the probability of an adverse health effect above the background probability of an adverse health effect given the condition that the individual would not have had the adverse health effect at the background dose (dose 0).

Table 4 is analogous to Table 3 except that the dose-response characteristics (ED_{10}, LED_{10}, q_1, and q_1^*) are quantified in terms of the added risk instead of extra risk.

In Table 4, using the added risk instead of the default of extra risk, including the available observation time data and the conservative low-dose linear extrapolation below the benchmark dose, but not including even a minimal adjustment for interspecies differences in background transition rates, the best estimates of the dose-response characteristics are

ED_{10} = 5.20 mg/kg/day in mice
-- geometric mean between males and females

q_1 = 0.13 added risk per mg/kg/day in humans
-- geometric mean between males and females

ED_{10} = 3.97 mg/kg/day in mice
-- worst case between males and females

q_1 = 0.17 added risk per mg/kg/day in humans
-- worst case between males and females

and the corresponding bounds are

LED_{10} = 4.24 mg/kg/day in mice
-- geometric mean between males and females

q_1^* = 0.16 added risk per mg/kg/day in humans
-- geometric mean between males and females

LED_{10} = 2.94 mg/kg/day in mice
-- worst case between males and females

q_1^* = 0.23 added risk per mg/kg/day in humans
-- worst case between males and females.

Table 4. Dose-response characteristics (ED_{10}, LED_{10}, q_1, and q_1^*) based on the liver adenoma and/or carcinoma incidence data in the NCI toxaphene mouse oncogenicity study (1979) and the pathology working group (PWG) findings: added risks

Liver Adenoma and/or Carcinoma Data in Mice	Maximum Likelihood Estimates		Bounds: 95% Confidence Limits	
	ED_{10} mg/kg/day in mice	Slope (q_1) per mg/kg/day in humans[1]	LED_{10} mg/kg/day in mice:	Upper Bound on Slope (q_1^*) per mg/kg/day in humans[1]
		Slope (q_1) to Added Risk at 1×10^{-6} mg/kg/day	Lower Bound on ED_{10}	Slope (q_1^*) to Added Risk at 1×10^{-6} mg/kg/day
		Slope (q_1) to Added Risk at ED_{10}		Slope (q_1^*) to Added Risk at LED_{10}
Minimal Adjustment for Interspecies Differences in Background Transition Rates				
Including Data on Observation Time				
Male	3.97	4.1×10^{-9}	2.94	7.3×10^{-9}
		0.0023		0.0031
Female	6.81	1.8×10^{-9}	6.11	2.3×10^{-9}
		0.0018		0.0020
Excluding Data on Observation Time				
Male	2.09	0.0043	0.96	0.011
Female	6.07	3.4×10^{-10}	4.33	0.0018
NOT Adjusted for Interspecies Differences in Background Transition Rates				
Including Data on Observation Time				
Male	3.97	3.0×10^{-7}	2.94	5.4×10^{-7}
		0.17		0.23
Female	6.81	1.0×10^{-7}	6.11	1.3×10^{-7}
		0.098		0.11
Excluding Data on Observation Time				
Male	2.09	0.32	0.96	0.81
Female	6.07	1.9×10^{-8}	4.33	0.10

[1] Interspecies extrapolation of cancer potency from mice to humans based on default assumption of interspecies equivalence on the (body weight)$^{3/4}$ scale

NCI Bioassay Dose Levels

In the NCI mouse study (1979), the initial dose levels in the two treatment groups were 160 and 320 ppm. At the end of 19 weeks, these dose levels were lowered to 80 and 160 ppm, respectively. At the end of 80 weeks, these dose levels were lowered to zero; that is, dosing was discontinued. The study duration was approximately 91 weeks.

The time-weighted average ppm levels were

$$[\ 160 \text{ ppm} \times 19 \text{ weeks} + 80 \text{ ppm} \times 61 \text{ weeks} + 0 \text{ ppm} \times 11 \text{ weeks}]\ /\ [\ 91 \text{ weeks}\ ] = 87.033 \text{ ppm}$$

and

$$[\ 320 \text{ ppm} \times 19 \text{ weeks} + 160 \text{ ppm} \times 61 \text{ weeks} + 0 \text{ ppm} \times 11 \text{ weeks}]\ /\ [\ 91 \text{ weeks}\ ] = 174.066 \text{ ppm}.$$

Using the current standard conversion for mice of 0.15 mg/kg/day per ppm in the diet implies that the two treatment groups had lifetime average daily doses (LADDs) of

$$87.033 \text{ ppm} \times [\ 0.15 \text{ mg/kg/day per ppm}\ ] = 13.055 \text{ mg/kg/day}$$

and

$$174.066 \text{ ppm} \times [\ 0.15 \text{ mg/kg/day per ppm}\ ] = 26.110 \text{ mg/kg/day}.$$

Default Interspecies Extrapolation

The current default assumption for the interspecies extrapolation of the cancer potency (q_1 or q_1^*) from animals to humans is to assume that the species will respond equivalently if exposed to the same dose on the mg/(kg)$^{3/4}$/day scale; that is, interspecies equivalence on the (body weight)$^{3/4}$ scale. Using the standard default body weight of 0.03 kg for mice and 60 kg for humans, the current default assumption for the interspecies extrapolation of the cancer potency (q_1 or q_1^*) from mice to humans would imply that the human cancer potency is 6.687 times greater than the mouse cancer potency since

$$(\ 60 \text{ kg}\ /\ 0.03 \text{ kg}\ )^{0.25} = 6.687.$$

2. Conclusions Concerning the Cancer Potency for Toxaphene

Using current EPA default methodology and the available data in the NCI toxaphene mouse oncogenicity study (1979) along with the pathology working group (PWG) findings, the quantitative cancer potency characterization for toxaphene is

$q_1^* = 0.16$ extra risk per mg/kg/day in humans.

This upper bound on the cancer potency for toxaphene is based on the most sensitive response in the animal bioassays; namely, liver adenoma and/or carcinoma in mice. The calculation of this upper bound includes the data on the time of the observation of each mouse, the conservative low-dose linear extrapolation below the benchmark dose (the LED_{10}), and the current default procedures for interspecies extrapolation between mice and humans.

The derivation of this upper bound on the cancer potency for toxaphene has been presented in Section 1 of this Appendix. Table 1 contains the summary of the experimental data in the NCI toxaphene mouse oncogenicity study (1979) along with the pathology working group (PWG) findings. Tables 2, 3, and 4 explicitly indicate the values corresponding to alternative calculations of the dose-response characteristics (ED_{10}, LED_{10}, q_1, and q_1^*) for toxaphene based on the liver adenoma and/or carcinoma data.

The upper bound (q_1^*) for toxaphene would not have changed if it had been based on added risk (Table 4) rather than the EPA default of extra risk (Table 3).

The upper bound (q_1^*) for toxaphene would have increased 1.8 fold from 0.16 to 0.29 if the data on the observation time of each mouse was ignored (Table 2).

The upper bound (q_1^*) for toxaphene would have decreased 600,000 fold from 0.16 to 2.7×10^{-7} if the slope of the extra risk would have been evaluated at a low dose corresponding to an upper bound on potential human exposures (e.g., 1×10^{-6} mg/kg/day) rather than being characterized by the slope of a linear extrapolation below the LED_{10} (Table 2).

The upper bound (q_1^*) for toxaphene would have decreased approximately 60 fold from 0.16 to 0.0025 if even a minimal adjustment were made for interspecies differences in the background transition rates from stage to stage in the multistage carcinogenic process. (In Table 3, the geometric mean of $q_1^* = 0.0031$ for males and $q_1^* = 0.0020$ for females is 0.00249).

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APPENDIX 7

CANCER CLASSIFICATION OF TOXAPHENE AND RISK ASSESSMENT ENDPOINTS

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CANCER CLASSIFICATION OF TOXAPHENE AND RISK ASSESSMENT ENDPOINTS

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APPENDIX 7:
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I. WEIGHT-OF-THE-EVIDENCE (WOE)

The following factors concerning the toxicology of toxaphene should be considered by EPA in determining the Weight-of-the-Evidence (WOE) of its oncogenic potential.

1. $B6C3F_1$ mice (55/sex/group) were administered toxaphene in the diet as dosage levels of 0, 7, 20, and 50 ppm for a period of 18 months, at which time they were placed on control diet for an additional 6 months (Litton, 1978). The highest dose level tested in this study did not elicit any toxicity as determined by mortality, clinical signs of toxicity, and histopathology and, therefore, did not meet EPA's criteria as an adequate dose level for oncogenicity testing. However, at this dose level in male mice only, there was a statistically significant increase in combined liver tumors ($p<0.05$). The incidence of adenomas, carcinomas, and total liver tumors was well within the historical control range for this tumor type.

2. In another long-term feeding study in $B6C3F_1$ mice (NCI, 1979), toxaphene was fed in the diet to groups of mice (50/sex/group) at dosage levels of 0, 99, and 198 ppm (time-weighted averages) for a period of 80 weeks. The mice were then placed on control diet for an additional 10 to 11 weeks. The dosage levels were reduced at week 19 because of several deaths. Because of the changes in dosage levels during the study, it is difficult to determine if dosing was excessive—above a maximum tolerated dose (MTD)—throughout the study; however, the Tarone test for a dose-related trend in mortality, when applied to Kaplan and Meirer curves, estimates that the probabilities of survival for male and female mice in this study were positive. A statistically significant increase in liver tumors (both benign and malignant) was seen in male and female mice at both dose levels. A reevaluation of the liver slides from this study by a PWG according to today's liver tumor diagnostic criteria was performed. The PWG found that most of the tumors diagnosed as carcinomas were adenomas, so that the tumors induced by toxaphene were found to be mostly benign. The incidence of liver tumors in this study was outside of the NCI historical control range.

3. Osborne-Mendel rats (50/sex/group) were fed toxaphene in the diet at dosage levels (time-weighted averages) of 0, 556, and 1112 ppm for males, and 0, 540, and 1080 for females for a period of 80 weeks, and then placed on control diet for an additional period of 30 weeks (NCI, 1979). Dosage levels were decreased twice during the study for male rats and once for females because of excessive toxicity (hyperactivity and generalized body tremors). Similarly, in the mouse NCI study, because of the changes of dose levels during the study, it is difficult to determine if dosing was excessive; however, because generalized tremors were seen at up to 52 weeks, the high-dose level was very likely excessive. Nevertheless, a statistically significant increase in thyroid (follicular cell) tumors was seen at the high-dose level in both males and

females. Only benign thyroid tumors were seen in female rats. In male rats, two malignant tumors were diagnosed; however, the preponderance of tumors (7/ 35 in the low dose group and 7/ 41 in the high-dose group) was benign. A slight increase in kidney tumors was also seen only in male rats.

4. ARS Golden Syrian hamsters (51/sex/group) were administered toxaphene in the diet for 21.5 months (males) or 18 months (females) (Litton, 1979). The dosage levels tested were 0, 100, 300, and 1000 ppm. Dosing was adequate for males as evidenced by effects on body weight gain and histopathology. Toxaphene was not oncogenic in the hamster study.

5. Results of mechanistic studies indicate that the thyroid tumors in rats are induced through a perturbation of the hypothalamic-pituitary-thyroid (HPT) axis by a mechanism that is nonlinear, that the kidney tumors in male rats are induced through alpha-2u-globulin (a mechanism that is not relevant to man), and that the liver tumors in mice are likely induced through a mechanism other than through effects on peroxisome proliferation or through DNA adduct formation. Toxaphene is a hepatic microsomal enzyme inducer similar to PB, which plays a role in the induction of thyroid tumors in rats and most likely of the liver tumors in mice as well. Microsomal enzyme inducers appear to induce liver "tumors" of a different histologic type than those liver tumors occurring spontaneously or through a genotoxic mechanism (Butler, 1996).

6. The results of the mutagencity testing that has been conducted on toxaphene are mixed, similar to those found for PB (McClain, 1990).

7. In subchronic and chronic toxicity testing in rats (Treon et al., 1952; Lehman, 1952; Ortega et al., 1957) and dogs (Lackey, 1949; Treon et al., 1952; Lehman, 1952), the primary target organ for toxaphene is the liver. Toxaphene is not a reproductive toxicant in rats (Kennedy et al., 1973) or mice (Keplinger et al., 1970), although it does have weak estrogenic activity at or near lethal dosage levels in the rat (Bioqual, Inc., 1997).

II. ONCOGENICITY CLASSIFICATION

Hercules believes that toxaphene should be classified as either a Category C oncogen (EPA, 1986) or a "not likely" human carcinogen according to EPA's proposed guidelines (EPA, 1996a) and that it should be regulated as a nonlinear threshold carcinogen. The basis for Hercules' belief arises from the following factors, which are discussed in more detail in the foregoing section:

- Toxaphene administration to male and female mice results in a statistically significant increase in benign liver tumors only at dosage levels that were likely in excess of an MTD.

- Toxaphene administration to male and female rats results in a statistically significant increase in thyroid tumors, and a slight, non-statistically significant increase in male kidney tumors at a dose level that is likely in excess of an MTD.
- The mouse liver tumors do not appear to be induced either through enhancement of peroxisome proliferation or a direct action of toxaphene on DNA.
- Mouse liver tumors induced by microsomal enzyme inducers are histologically distinct from those spontaneously produced and from those induced through a genotoxic mechanism; toxaphene is a microsomal enzyme inducer.
- The slight increase in male rat kidney tumors is induced by a mechanism that is not relevant to man.
- The male and female rat thyroid tumors occur through a mechanism that has a nonlinear threshold; in addition, these tumors were seen at a dosage level that is very likely in excess of an MTD (tremors at 52 weeks).
- Toxaphene is negative for oncogenicity in the hamster.
- The results of mutagenicity testing on toxaphene are mixed, but the majority of the study results are negative.

According to EPA's proposed Carcinogen Risk Assessment Guidelines (1996a), these factors support a "not likely" human carcinogen classification because the toxaphene-induced tumors occur at a dosage level that is in excess of an MTD by a nonlinear mechanism (rat thyroid) or by a mechanism that is not relevant to man (rat kidney), or are primarily benign tumors that are commonly occurring and are seen at dosage levels that are likely excessive (mouse liver).

III. DETERMINATION OF THE NO OBSERVED EFFECT LEVEL (NOEL) FOR AN MOE ASSESSMENT AND OF AN LED_{10}

Hercules believes that the appropriate NOEL to use for an MOE assessment for general toxicity is 25 ppm, which is the NOEL in rats for liver toxicity (absolute and relative weights and fatty vacuolization) in both a two-year feeding study (Treon et al., 1952) and in a rat reproduction study (Kennedy et al., 1973). The next highest dose level tested in both of these studies was 100 ppm. The NOEL that was used for the reference dose (RfD) setting by EPA (Health Effects Division; Office of Pesticide Programs Reference Dose Tracking Report, April 14, 1995) was derived from a two-year feeding study in dogs. The NOEL in this study was 10 ppm based on slight liver degeneration seen at 100 ppm toxaphene. Because the NOEL for liver effects in both rats and dogs appears to be less than 50 or 100 ppm but greater than 10 ppm in dogs and 25 ppm in rats, Hercules selected 25 ppm (approximately 1.25 mg/kg/day in rats and 0.65 mg/kg/day in dogs) as being closest to an actual NOEL for risk assessment purposes.

An LED_{10} for toxaphene was calculated based on two different endpoints: liver carcinomas/adenomas incidence data in male and female mice. These values are summarized in Table 1 and their derivation can be found in Appendix 6 (Quantitative Dose-Response Assessment for Toxaphene).

Table 1. LED_{10}'s for Toxaphene from Rat and Mouse Studies

Study/Endpoint	LED_{10} (mg/kg/day)	Geometric Mean
oncogenicity study in mice		
males		
carcinomas/adenoma	2.87	
females		4.19
carcinoma/adenoma	6.11	

Hercules proposes that the geometric mean LED_{10} of 4.19 mg/kg/day be used by EPA for liver tumor risk assessment purposes.

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References

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